

THE CH LLE GE OF D ABETES
Acute and almost s multaneo s et of diabetes in dent al
t ns aged ½ years

THE CLINICAL SYNDROME OF DIABETES MELLITUS

BY

JOHN LISTER
M A M D M R C P (Lond)

With 34 illustrations



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FOREWORD

It is and ever will be a source of pride that the first stirring of interest in the disorder diabetes mellitus increasing over the years to the final yield of this volume was first aroused while John Lister was working amongst diabetics at the Royal Free Hospital

Here is a thoughtful and thoroughly competent work Wide experience deep enthusiasm and depth of vision stand out from the pages The whole field of manifestation and management of this common and complicated disease is covered in a way at the same time interesting and informative yet easy to read All that the student and family doctor needs is here Those more informed can still gain by reading the text while the generous bibliography and useful break up into three clear divisions add to its value as a book of reference

It is both a pleasure and a satisfaction to be associated with this book which will serve to keep fresh the memory of many happy years of work with its stimulating young author

The Royal Free Hospital UNA LEDINGHAM



PREFACE

THE successful care of diabetic patients demands a certain conviction and considerable enthusiasm on the part of the clinician in charge. Unfortunately few conditions cause more anxiety to students and practitioners than diabetes and at present there seems to be a lack of a small textbook covering the essential clinical aspects of the disease.

The aim of the present volume is to assist students in their understanding of the many clinical variations of the syndrome and to assist practitioners in the management of cases. The emphasis is almost entirely clinical and no attempt has been made to consider in detail the more fundamental physiological biochemical and endocrine aspects of the diabetic syndrome. The views expressed are partly those gained by personal experience in diabetic clinics and partly those held by many clinicians who are interested in the treatment of diabetics.

The book has been divided into three parts: the first concerned with the diagnosis and treatment, the second with the many associated conditions and complications, and the third with the medico social aspects of the disease. Each chapter has been prepared so that it may be separately read for easy reference. Because of personal experience some aspects of the condition have received more emphasis than others. Thus the constitutional factors and the many ophthalmic manifestations have been specially stressed but at the same time most of the important aspects of the clinical syndrome have been mentioned and for those wishing further information a full bibliography has been provided.

My own interest in diabetes was first stimulated by working with Dr Una Ledingham in the Diabetic Clinic at the Royal Free Hospital and I am glad to have this opportunity of thanking her for her many kindnesses and continued encouragement and for permission to use much data collected in her clinic. I am also grateful for the special experience

gained in the ophthalmic aspects of diabetes in the Physician's Clinic at Moorfields Eye Hospital. Many others have helped me in the preparation of this book. These include Dr Doreen Allan who greatly assisted me in the preparation of the text and in reading the manuscript; Dr H J Galbraith who helped to supply much of the data in Chapter III; Dr John Nash who wrote the chapter on Carbohydrate Metabolism and Mr Dennis Vobes who wrote the technical part of the chapter on practical procedures. I am grateful to Dr Norman Ashton for his photographs of the retinal and renal lesions in diabetics and to Mr E F Fincham of the Institute of Ophthalmology for his photograph of diabetic cataract and to Miss D Bannister for the many photographs she has taken of my Windsor patients. I must also thank the editors and authors who have allowed me to reproduce tables and illustrations as indicated in the text and my publishers for the trouble they have taken to meet my wishes. Finally I must thank my wife for her patience and encouragement in the preparation of this book.

April 1959 J L

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THE CLINICAL SYNDROME OF DIABETES MELLITUS

PART I

DIAGNOSIS AND TREATMENT

CHAPTER I

INTRODUCTION

THE clinical picture of a wasting disease associated with thirst and polyuria has been recognized from earliest times In fact the oldest medical document in existence—the papyrus Ebers which was discovered in Egypt in 1862 and dated by archaeologists as about 1500 B C describes a condition characterized by an abnormal polyuria The name diabetes was first used by the Greek physician Aretaeus of Cappadocia who lived in the second century The word is ionic Greek the literal translation being to run through a siphon In addition to giving the disease its name Aretaeus described the rapid downhill course of a severe case According to the translation of Papaspyros he wrote Diabetes is a wonderful affection not very frequent among men being a melting down of the flesh and limbs into urine The patients never stop making water but the flow is incessant as if the opening of aqueducts Life is short disgusting and painful thirst unquenchable excessive drinking which however is disproportionate to the large quantity of urine for more urine is passed and one cannot stop them either from drinking nor making water Or if for a time they abstain from drinking their mouth becomes parched and their body dry the viscera seems as if scorched up they are affected with nausea restlessness and a burning thirst and at no distant term they expire

Other early physicians were also aware of the condition notable amongst these being Galen who described diabetes as a weakness of the kidney which cannot hold back water

It was however not only in the early Greek civilization that diabetes was recognized The Chinese and Japanese of the third century were well acquainted with it and noted that the urine was sweet and attracted dogs The early Hindus were also familiar with a condition in which the urine had a sweet taste and looked like honey and the fifth century physician Susruta even suggested that over-eating might pre cipitate the malady Because of the characteristics of the urine the Indian name for diabetes came to be Madhumeha meaning honey urine

Centuries later the great Arab physician Avicenna (980–1027) described diabetes with great accuracy He noted that his diabetic patients complained of thirst an inability to work and a loss of sexual potency Some of them had en larged livers and others developed carbuncles gangrene and phthisis In spite of these early clinical descriptions of the disease there was no real attempt to explain its cause al though both Aretaeus and Avicenna had suggested that there might be primary and secondary types The Hindus had reported the association of the disease with obesity and the sweetness of the urine had frequently been noted The im portance of the last observation seems to have been over looked for many centuries until Thomas Willis (1621–75) of Oxford stressed its significance and although it was William Cullen (1710–90) who was the first to add the adjective mellitus it was Willis who differentiated diabetes mellitus from diabetes insipidus He pointed out that the latter pre sented no glycosuria and suggested that in the Pissing Evil sugar appears first in the blood and then in the urine

The association of diabetes with pancreatic disease was first noted by Cawley (1788) when he reported a case in which he found glycosuria during life and pancreatic calculi at autopsy Brunner (1683) had already noted that pancreatec tomy in the experimental animal caused thirst and polyuria but he did not appreciate the significance of the observation and it was not until Von Mering and Minkowski (1889)

demonstrated that pancreatectomy in dogs caused hyperglycaemia glycosuria and death that the relationship between the pancreas and diabetes mellitus was fully recognized The earlier workers may have been confused by the fact that until Langerhans (1869) noted the presence of the islet cells which now bear his name the pancreas was considered as a gland of external secretion related only to digestion Indeed it was only after the work of Von Mering and Minkowski that real interest was aroused in determining the function of the islet cells

Opie (1901) while carrying out a series of autopsies on diabetics discovered a hyaline degeneration of the islet cells and Ssobelew (1902) in the same year made a similar observation and found further that after the ligation of the excretory ducts of the pancreas in an experimental animal the acinous tissue gradually atrophied while the islet cells remained intact MacCallum (1909) confirmed this latter observation and also noted that if the islet cells escaped damage during the experimental procedure no diabetic symptoms developed but if the islets were injured classical diabetic symptoms appeared

These were the vital steps which led to the final isolation by Banting and Best (1922) of the hormone secreted by the islets of Langerhans Earlier workers had succeeded in preparing alcoholic pancreatic extracts Indeed Zuelzer (1908) prepared such an extract which had a favourable effect on the hyperglycaemia of depancreatized dogs but unfortunately the extract was impure and its injection caused rigors Banting realized that it was essential to have a pure islet cell extract and he devised a technique which caused a complete degeneration of the acinous part of the gland leaving the islets unharmed and enabling him to prepare from them a pure extract This hormone when injected into diabetic dogs was found to lower the blood sugar level "At first known as isletin, the hormone soon came to be called insulin" the name by which Sir Edward Sharpey Schafer (1916) of Edinburgh had previously suggested that the hypothetical substance secreted by the islet cells of the pancreas and probably controlling the mechanism of carbohydrate metabolism should

be known The isolation of insulin was the culmination of centuries of clinical observation and years of experimental *physiology* For the diabetic it was the most important achievement in the history of medicine while for the clinician and the physiologist it produced new and fascinating problems

Two of the most fundamental of these were the mode of insulin action and the relationship between the islet cells of Langerhans and other glands of internal secretion The association between glycosuria and intracranial lesions had been recognized ever since Bernard (1849) had noted its occurrence after piqure of the floor of the fourth ventricle and clinicians had observed a high incidence of diabetes in patients with acromegaly Thus Hansemann (1897) found that 11 per cent and Borchardt (1908) found that 35 5 per cent of his acromegalics had diabetes mellitus Cushing and Davidoff (1927) found that 25 per cent of their acromegalic patients had glycosuria and 12 per cent had frank diabetes These workers suggested two hypotheses for the cause of diabetes mellitus in acromegaly firstly that the pituitary tumour caused pressure on a sugar centre in the hypothalmus and secondly that there was an endocrine cause *The first theory* was rejected as the size of the tumour in acromegaly bears no relation to the incidence of glycosuria and they considered that hyperpituitarism was the cause of the glycosuria of acromegaly There was already experimental evidence to support this hypothesis as Crowe Cushing and Homans (1910) had noted that the sugar tolerance of animals was increased by hypophysectomy and also that the hyperglycaemia caused by the removal of a large portion of the pancreas tended to subside when a partial hypophysectomy was subsequently performed Although these workers suspected that the anterior lobe of the pituitary was at fault in these cases it was Houssay and Biasotti (1931) who confirmed this beyond doubt They showed that in toads if the pituitary is removed pancreatectomy does not provoke glycosuria but that severe diabetes develops if an anterior lobe is implanted beneath the skin on the following day Subsequently these workers studied the effects of hypophysectomy

and pancreatectomy on dogs cats toads and other animals Houssay (1936) reported that the usual syndrome of pancreatic diabetes in mammals undergoes numerous changes following hypophysectomy Most important amongst these changes are the diminution of glycosuria and polyuria the disappearance of ketosis and the development of hypersensitivity to insulin Houssay also considered the relationship of the islet cells of the pancreas to the thyroid and suprarenal glands (Glycosuria is well known to occur in hyperthyroidism but Houssay found that thyroidectomy does not alleviate experimental pancreatic diabetes) He showed that the injection of anterior pituitary extract into hypophysectomized pancreatectomized amphibians particularly the toad produced diabetogenic effects and furthermore that these effects are still obtained in the absence of the thyroid and suprarenal glands He thus established that the anterior pituitary can produces diabetes independently of any other endocrine disturbance but he failed to show that a permanent diabetic state could be produced experimentally by injections of anterior pituitary extract

Permanent diabetes was however observed to develop with such injections by Young (1937) While investigating the effect of anterior pituitary extract on dogs he found that two animals became diabetic and remained so after the injections were stopped

A clear relation between the anterior pituitary and diabetes having thus been established the problem remained as to how insulin facilitated carbohydrate metabolism and in what way the balance of anterior pituitary diabetogenic effect against insulin is maintained in the normal economy of the body The nature of this balance has partly been elucidated by the work of Cori (1945) who pointed out that in the path of intracellular carbohydrate metabolism there are certain obligatory stages through which the metabolic stream must pass One of the most important of these is the conversion of glucose into glucose 6 phosphate once this substance has been formed the synthesis of glycogen and the whole chain of reactions involved in carbohydrate oxidation becomes possible even in diabetic animals The reaction is facilitated by

the enzyme adenosine triphosphate and Cori has shown that it is catalysed by the enzyme hexokinase and further that *in vitro* the hexokinase reaction is inhibited by anterior pituitary extract and that this inhibition is counteracted by insulin Insulin and anterior pituitary extract thus appear as regulators of those basic reactions which dispose of glucose

The varying ways in which patients respond to insulin remained an obstacle to the complete understanding of the mechanism for shortly after the introduction of insulin into medical practice it became clear to clinicians that some diabetic patients are relatively refractory to its effect

In general, such differences have been regarded as the result of complicating factors which superimpose a relative resistance to insulin on the basic disease of diabetes mellitus Temporary resistance occurs with infections thyrotoxicosis and unsuitable diets but it is difficult to explain the persistent difference in insulin sensitivity between apparently uncomplicated cases of diabetes

Falta (1936) suggested that diabetics are of two types—insulin sensitive and insulin resistant He substantiated this by showing that different diabetics require varying amounts of insulin to prevent the excretion of urinary sugar under standard conditions Similarly Himsworth (1936) investigated the insulin sensitivity of a series of diabetic patients and he found that they tended to fall into two distinct groups—the frankly sensitive and the frankly insensitive and that intermediate degrees of sensitivity were rare He found that in general the patients giving the sensitive response were young and thin with healthy arteries and a normal blood pressure, and that in such cases the disease was severe and of sudden onset but responded to insulin They were found to be liable to both ketosis and to hypoglycaemia He suggested that the possible explanation of such a finding was that in those cases which gave a sensitive reponse to his test the diabetic state was due to a deficiency, while in the cases which gave an insensitive response the diabetic state was due rather to some interference with the action of insulin

This hypothesis is supported by observations made by Ricketts Brunschwig and Knowlton (1945) and by Lawrence

(1949) Ricketts Brunschwig and Knowlton (1945) reported a case of carcinoma of the head of the pancreas treated by total pancreatectomy in which the resultant diabetic state was controlled by a diet containing 400 G carbohydrate and a daily insulin dosage of only 40 units Lawrence (1949) observed that the young insulin sensitive diabetic eventually comes to require a daily dose of 40–60 units of insulin representing a state of absolute diabetes which would appear to result when all the pancreatic islets have ceased to function Many diabetics however require much larger doses of insulin to control the blood sugar level and prevent ketosis and this would suggest that in some diabetic subjects there must be factors at work other than pure insulin deficiency

Further support for this view has come from Bornstein and Lawrence (1951) These workers were able to demonstrate a fall in the blood sugar of hypophysectomized adrenalectomized rats with insulin doses as low as 50 micro units Using this technique they were able to show that the plasma of five diabetic patients who were clinically responsive to insulin therapy was deficient of insulin whereas the plasma of five diabetics who were clinically unresponsive to such therapy contained insulin in normal amounts

Recently it has been possible to estimate plasma insulin activity more easily by the rat diaphragm method (Gemmill 1941 Stadie and Zapp 1947 Krahl and Park 1948 Groen *et al* 1952 Vallance Owen and Hurlock 1954 Randle 1954)

With this method Vallance Owen *et al* (1955) found similar results to those of Bornstein and Lawrence Thus they found that a group of their acute diabetic patients who required insulin to prevent ketosis, demonstrated no plasma insulin activity whereas a group of mild obese diabetic patients had almost normal amounts of circulating insulin This observation suggests that in the obese group there must be some factor causing inhibition of the action of insulin but its nature is not yet fully understood On the other hand although Wrenshall *et al* (1952) *found a much lower extractable insulin* content in pancreatic material obtained at autopsy from young diabetics than in those who developed diabetes in

later life these workers considered that much work has still to be done before the full significance of an insulin insensitive type of case can be fully assessed

Nevertheless from the clinical viewpoint two clear types of diabetic patient may be identified First there is the patient who is frankly and absolutely deficient in insulin This patient is *often young but may be of any age and of* either sex and usually presents with acute diabetic symptoms which are liable to progress to ketosis and diabetic pre-coma or coma if insulin *replacement* therapy is not *rapidly* instituted *and maintained Secondly there is the patient* whose insulin deficiency *is* relative and not absolute and *in* whom the deficiency may remain marked for a considerable period of time before diagnosis Such patients are usually obese and *most characteristically they are* middle aged *women In* these cases the presentation is only rarely with the frank diabetic symptoms of thirst and polyuria but much more frequently it is with pruritus vulvae or with some diabetic complication *In these cases* weight reduction *is the most* important single therapeutic measure and insulin therapy should be avoided if possible because in many cases the impaired carbohydrate tolerance is greatly improved after weight *reduction* (*see* Fig III 4) and *insulin* therapy tends to maintain the weight and even *encourages further weight gain*

Unfortunately both groups of patients are liable to the same diabetic complications with the exception of dangerous ketosis which only occurs when there is a state of absolute *insulin deficiency*

At the same time *it* must be appreciated that there is bound to be a certain degree of overlap of the two types *of* case and there is much to be said for the suggestion made by Himsworth (1949) that *diabetes* should be regarded as a syndrome *rather than as a single entity*

Certainly there *is* no better population than the patients attending a diabetic clinic in whom to study the natural history of disease Many become life long attenders and apart *from the important matters of* prescribing insulin and checking diet the family histories *of the patients the* varying modes of presentation and the endless associated condi

tion and complications which manifest themselves over an extended period provide a wealth of interest and experience for the diabetic physician Indeed it has been said that one who knows diabetes and all its complications knows medicine (Winnett 1939)

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CHAPTER II

CARBOHYDRATE METABOLISM

by JOHN NASH

In primitive forms such as yeasts carbohydrate metabolism is an independent intracellular group of reactions but in higher animals carbohydrate metabolism is much more complex and forms a link between the other physiological functions of the body Carbohydrate, in addition to being a basic food stuff, is a vehicle for the transport of energy for specialized organ activity and for storage of food in other chemical forms It is intimately correlated with numerous vital chemical reactions so that the term carbohydrate metabolism should not be regarded as a reference to a single metabolic process At the same time for research purposes it has been necessary to try to isolate certain processes for study and then fit the resulting information into a comprehensive scheme the purpose of this chapter is to summarize our fundamental knowledge of the carbohydrate aspects of metabolism in such a way as to be helpful to clinicians in understanding diabetes mellitus In the course of evolution from primitive organisms with anaerobic respiration to highly complex forms such as man with special digestive respiratory locomotor and excretory organs carbohydrate has remained an essential food stuff It is useful therefore to review in general terms our advances in knowledge of intermediary carbohydrate metabolism during the past century because an appreciation of the biological significance of carbohydrate metabolism may help in our understanding of the special arrangements which exist in man

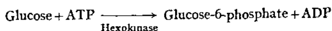
In 1860 Pasteur showed that yeast was essential for the alcoholic fermentation of carbohydrate and he subsequently showed that yeast could ferment in the absence of free oxygen thus demonstrating anaerobic respiration for the first time

In 1897 Buchner showed that sucrose can be fermented in the presence of yeast juice but in the absence of living yeast cells this ability of yeast juice to ferment sucrose to *alcohol carbon dioxide and water was recognized as the* action of an organic catalyst which was called zymase This was in fact the first known enzyme although it was soon discovered that zymase consisted of a complex collection of *enzymes Following these fundamental discoveries* research into the intermediary metabolism of carbohydrate has continued intensively ever since

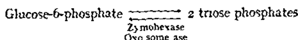
Harden and Young (1905) showed that the rate of fermentation of glucose by zymase diminished after a time but that the addition of phosphate restored activity which again fell off as the concentration of phosphate declined This suggested that phosphate combined with sugar to form an ester which they were able to isolate as hexose diphosphate Later Robison (1922) isolated glucose 6 phosphate which subsequently proved to be an intermediate ester of great importance in carbohydrate metabolism It was recognized that enzymes were protein in nature but Harden and Young (1906) soon discovered that a non protein dialysable compound was essential for yeast juice activity This substance was called co enzyme 1 and it was found to act by combining with hydrogen atoms removed from intermediate products by enzymes called dehydrogenases This is a very important process because it permits an oxidative process to proceed in the absence of free oxygen This co enzyme 1 was subsequently found to be vitamin B1

In succeeding years many intermediate steps in yeast fermentation were elucidated by workers such as Emden Meyerhof Needham and the Coris Harden and Young (1908) found that adenosine triphosphate (ATP) acted in yeast metabolism as a carrier of phosphate which it could release with a transfer of energy

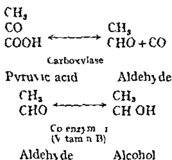
The complex series of reactions which occur in yeast fermentation can be summarized as follows



Various enzyme actions occur which result in the breakdown of glucose 6 phosphate to 3 carbon compounds called triose phosphates



These triose phosphates undergo a complex series of enzyme reactions to produce phospho pyruvic acid which is an important substance in carbohydrate metabolism this substance gives up its phosphate to reform adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and forms pyruvic acid By means of the enzymes dehydrogenase carboxylase and co-enzyme I (vitamin B1) final oxidization to alcohol and carbon dioxide occur



In the absence of vitamin B1 pyruvic acid accumulates on the medium This also holds true in human carbohydrate metabolism so that in vitamin B deficiency there is an excess of pyruvate in the blood

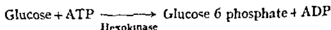
Concurrently with the studies on yeast similar work was being carried out on muscle and liver metabolism In 1907 Fletcher and Hopkins working on the frog showed that lactic acid is produced when muscle is stimulated In 1924 Myerhof showed that glycogen changes quantitatively into lactic acid during muscular contraction As in yeast phosphate was found to be essential for muscle metabolism and it was shown that creatine phosphate was present in muscle and was broken down during muscle contraction

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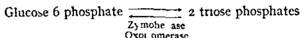
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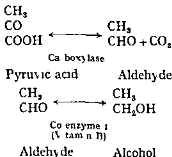


$$\text{Glucose} + \text{ATP} \xrightarrow[\text{Hexokinase}]{} \text{Glucose 6 phosphate} + \text{ADP}$$

Various enzyme actions occur which result in the breakdown of glucose 6-phosphate to 3 carbon compounds called triose phosphates

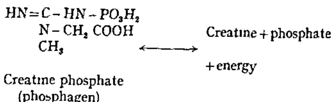


These triose phosphates undergo a complex series of enzyme reactions to produce phospho-pyruvic acid which is an important substance in carbohydrate metabolism this substance gives up its phosphate to reform adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and forms pyruvic acid By means of the enzymes dehydrogenase carboxylase and co enzyme I (vitamin B1) final oxidization to alcohol and carbon dioxide occur



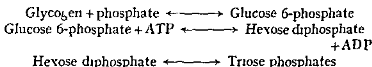
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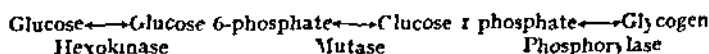
In 1929 Lohmann discovered adenosine triphosphate in muscle and showed that it is formed by the reaction of adenosine diphosphate with creatine phosphate Further work indicated that creatine phosphate acts as a store of energy in the form of phosphate Ultimately creatine is changed back to creatine phosphate by means of energy obtained from glycolysis of glycogen

Thus there is a striking similarity between muscle and yeast metabolism



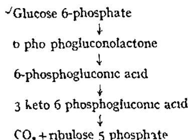
The triose phosphates undergo a similar series of reactions to those occurring in yeast to form pyruvic acid which under *the influence of co enzyme I forms lactic acid In resting* conditions of muscle no excess of lactic acid remains but in conditions of vigorous muscle activity lactic acid is conveyed to the liver where it is reconverted into glycogen

The liver cells contain numerous enzymes which catalyse the complex reactions for the metabolism and storage of carbohydrate as glycogen and also for interactions and interconversions with proteins and fat For example liver has the ability to carry out the following series of reactions



The above series of reactions which can probably be carried out anaerobically by all body cells are termed the Emden Myerhof pathway and until recently it was thought that the breakdown of glucose-6-phosphate to pyruvate mainly occurred in this way Recently another pathway

has been demonstrated and has been given various names including the hexose monophosphate shunt. It is probably only one of many alternative oxidative pathways which normally operate. The steps on this pathway are as follows:



The pentose thus formed provides a source for synthesis of ribose nucleotides, one of the numerous reactions which must occur in the liver and other organs.

In addition to these anaerobic processes the higher animals utilize a liberal supply of oxygen to achieve more efficient oxidative processes for the production of the energy essential for muscular activity. Szent Gyorgyi (1935, 1936) made an important observation which led to our present concept of aerobic metabolism of carbohydrate in both muscle and liver. He found that succinate and fumarate acted catalytically in the respiration of oxygenated muscle; as it was known that the dehydrogenases were enzymes concerned with these substances, it was clear that a reaction involving removal of hydrogen was taking place. Krebs (1937) suggested a citric acid cycle in which these substances acted catalytically combined with pyruvic acid and quantitatively produced carbon dioxide. This cycle (Fig. II, 1) has a number of important functions. It provides for aerobic oxidation of pyruvate and acetate and also of any intermediate substances of the cycle which come in contact with it from other sources. Acetic acid, which is an intermediary in fat metabolism, can take part in the catalysis and thus provide a mechanism for oxidation of fat. The three carbohydrates—pyruvate, oxaloacetic and oxoglutarate—which take part in the cycle can produce or arise from the amino-acids

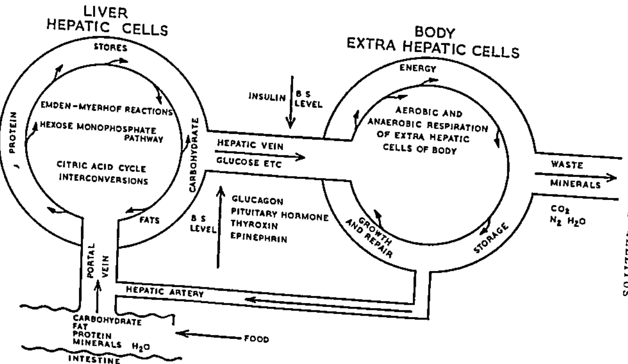


FIG II 1 —Metabol c pathways n carbohydrate metabolism

alanine aspartic acid and glutamic acid Thus an important link with protein metabolism is achieved

The higher animals need to be able to store carbohydrate in a form which is readily available and glycogen serves this function admirably Owing to the very large size and low viscosity and low osmotic properties of the glycogen molecule it has no serious physical effects on intercellular fluids It is readily changed to hexose 1 phosphate by a phosphorylase system The chemistry of glycogen synthesis and breakdown need not concern us here except to state that a branching enzyme transglucosidase plays an important part This results in a branching type of polysaccharide which is particularly suitable for rapid storage and utilization

The intermediary metabolism of carbohydrate which has been very simply outlined can be summarized in the diagram The effect of certain hormones in these processes have been indicated the major effects of insulin being balanced by the combined effects of the other hormones

Insulin Although certain general effects of insulin are very well known the precise methods and sites of action are still not clearly understood Some workers have maintained that the site of action of insulin is the cell membrane in the cells of peripheral tissues and that the effect on the liver is indirect The details of this controversy are beyond the scope of this chapter but it is undeniable that the following general actions of insulin are established

Pancreatic removal is followed by

(1) Hyperglycaemia
(2) Depletion of glycogen in liver and muscle
(3) Lower respiratory quotient
(4) Increased ketogenesis
(5) Increased gluconeogenesis

Increased supply of insulin is followed by

(1) Hypoglycaemia
(2) Increased glycogen storage
(3) Increased respiratory quotient

The main actions of insulin then appear to be

Acceleration of glucose oxidation including formation of fat and protein

Increase in formation of glycogen

These and other effects of insulin may depend on a single action of insulin either by accelerating transport of carbohydrate across cell membranes or by aiding an important reaction in the cells For example the well known effect in releasing hexokinase from anterior pituitary hormone inhibition may yet prove to be one of its important actions (Colowick *et al* 1947)

At the same time it is likely that the various hexokinases from different organ cells may vary in their substrates and also in their sensitivity to hormones From evolutionary considerations it might be anticipated that the action of insulin would be concerned with the aerobic respiration and transport of glucose rather than with the more primitive anaerobic processes and in general this appears to be so It seems probable that the effects of insulin on different groups of body cells may depend on varying sensitivities of enzymes to the numerous substances concerned in carbohydrate metabolism Such a broad concept of the significance of insulin is helpful in the treatment of diabetes mellitus

In view of these considerations the clinical phenomenon of insulin resistance is readily anticipated but correspondingly difficult to elucidate A large number of factors may cause insulin resistance and are listed as follows

(1) Poor absorption of insulin
(2) Metabolic disturbance by toxaemia
(3) Endocrine disorders such as hyperthyroidism hyperpituitarism and hyperadrenalism
(4) Excess anti insulin substances including glucagon
(5) Liver disease
(6) Excess insulinase
(7) Deficient circulating glutathione
(8) Insulin antibody formation

Glucagon From the metabolic aspect the most interesting of these factors is glucagon which was first identified by Kimball and Murlin in 1923 Glucagon is secreted in the pancreas possibly *in the alpha cells, and a similar substance* has also been identified in chromaffin cells of the intestine It has the effect of raising the blood sugar level by activating phosphorylase in the liver While the precise role of glucagon has yet to be established it seems likely that it acts in a homeostatic way in conjunction with insulin to maintain the blood sugar level It can readily be conceived that between periods of ingestion of food glucagon and insulin could readily balance their secretion through fluctuations in the blood glucose level Because glucagon does not appear to play so vital a role as insulin a clinical syndrome *of abnormal glucagon activity has not been identified as yet* though it is theoretically possible that certain types of diabetes mellitus could be due to over secretion of glucagon

Sufficient has been written to illustrate how the homeostasis of carbohydrate metabolism has been maintained in increasingly complex animal forms by balanced hormonal control of enzyme catalyzed intracellular reactions appropriately modified for each particular organ

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CHAPTER III

AETIOLOGY

Incidence It is difficult to determine accurately the frequency with which diabetes mellitus occurs It has been stated that there are more than a million known diabetics in the United States and that about 55 000 new cases are being identified each year (Marks 1947) In this country it has been estimated that there are about 150 000 known cases (Tunbridge 1953) In addition it is probable that there are almost equal numbers of undetected cases because whenever a detection drive has been carried out it has been shown that approximately one new case of frank diabetes is discovered for every previously known case

In the United States several such drives have been carried out Wilkerson and Krall (1947) carried out a survey in Oxford Massachusetts and examined the blood and urine of 3 516 persons and found 70 cases of diabetes 40 of whom were already known to be diabetic and 30 not previously recognized On this basis the incidence of diabetes in the United States would be 1 7 per cent of the population and although this figure may be rather high it is probable that the true incidence of diabetes is more than 1 per cent of the population Furthermore the number of recognized cases is continually increasing Several factors contribute to this Firstly the maximum number of cases are diagnosed during the sixth decade of life and the increased longevity of the population has caused an increasing number of persons of this age Secondly the medical profession have doubtless become more diabetes conscious and diagnosis is probably established earlier than previously Thirdly the increased longevity of the diabetic and the better management of pregnancy in diabetic women is resulting in the birth of more potential diabetics

Age Distribution In all large series of diabetics the greatest number of cases have been diagnosed during the sixth de

cade of life Barach (1949) found that in 1 000 diabetics the age at which most cases became manifest was between 51 and 55 and Wilkerson and Krall when carrying out their Public Health Survey in which they detected 30 new cases of diabetes mellitus in a population of 3 516 found that the

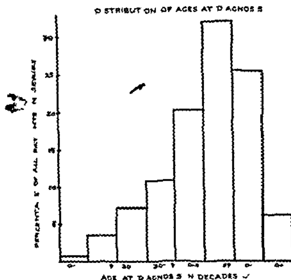


FIG III 1—Age at diagnosis in 3 8 patients at Royal Infirmary Hospital

average age of these cases was 55 years Similarly Pincus Joslin and White (1934) found that in a series of 4 639 male and 5 214 female cases the maximum onset occurred in the sixth decade the year of greatest susceptibility in the male being 51 and in the female 55

It would appear that almost a third of all cases are diagnosed between the ages of 50 and 59 over a half above the age of 50 and over three quarters above the age of 40 Nevertheless the disease may present at any period of life and cases have occasionally been recorded in infancy and they occur not infrequently in old age These observations

are well reflected in a small series of cases at the Royal Free Hospital (Fig III 1)

It is again important to stress that in most adults the onset is indefinite so that the age at the time of diagnosis does not necessarily correspond with the age at which carbohydrate metabolism became disordered Indeed in most cases it may be assumed that some degree of carbohydrate intolerance has existed for a variable and indeterminable time before diagnosis and Colwell (1942) considers that in many diabetics the full course of the disease is half run before the diagnosis is made

Sex Distribution Diabetes is more common in females than in males as may be seen from Table 1 which tabulates the sex incidence reported by workers from leading centres throughout the world It is notable that the only clinic

Table 1 THE SEX INCIDENCE IN DIAGNOSED DIABETICS

Author	*Date*	*Source*	*Number of Patients etc*	*Percentage of Women*
Altschul and Nathan	1942	Harlem U S A	639 (Negroes)	80
Munro *et al*	1949	Glasgow Scotland	1 309	69 3
Rudy and Keeler	1939	Boston U S A	1 376 (Jews)	64 6
Perrott *et al*	1939	National Health Survey U S A	9 182	64 2
Martin	1953	King s College Hospital London	4 105	64
Altschul and Nathan	1942	Harlem U S A	106 (Whites)	64
Aarseth	1953	Oslo Norway	312	59 9
Hanssen	1946	Bergen Norway	710	59 4
Barach	1949	Pittsburg U S A	2 505	57 9
John	1950	Cleveland Ohio	6 000	56 7
Dreyer and Hey	1953	Denmark	17 229	55 5
Broch and Klovstad	1947	Vestfold Norway	4 6	53 8
Dahlberg *et al*	1947	Sweden	15 519	53 1
Joslin *et al*	1952	Massachusetts	1 000	51
Wilder *et al*	1940	Mayo Clinic	1 998	43 5

which reports a higher proportion of male than female patients is the Mayo Clinic This may be due to the fact that this clinic does not draw its patients entirely from the local community but tends to attract patients from long distances and they are frequently of the business executive type and hence are usually male On the other hand Wilder *et al* (1940) suggested that the higher female incidence in series other than their own is due to the proportion of Jewish patients in these series and quote the female incidence of 64 6 per cent among 1 376 Jewish patients as reported by Rudy and Keeler (1939) This is probably only a minor factor in most series and it is more important to stress the fact that the increased proportion of women patients becomes most marked from the childbearing period until the menopause Indeed Mosenthal and Bolduan (1933) found that it was only among married women that there was any difference between the sex incidence of the disease

The effect of pregnancy the increase in weight which often follows childbearing and lactation and the generally better economic state of the married with consequent overnutrition are all factors which doubtless contribute to this increased incidence of diabetes in married women

Familial Incidence There is a strong familial incidence of diabetes and in about one third of all cases there will be obtained the history of a blood relative also being diabetic Barach found that 44 5 per cent of his patients gave a history of diabetes in blood relatives He admitted that this figure is higher than that mentioned by other workers but he considered that it would be higher still if the patients knew their family histories better On routine examination of 45 650 prospective recruits for the American armed forces Blotner Hyde and Kingsley (1943) found 208 cases of diabetes A positive family history for diabetes was given by 32 per cent of these men as compared with 5 2 per cent of a similar group of non diabetics who were questioned for control purposes

The mechanism of the hereditary factor in diabetes is not yet fully understood White and Pincus (1934) have suggested that the potentiality for developing diabetes may be

transmitted as a recessive Mendelian characteristic while others have postulated a single semi dominant gene as a determining factor and others again think that on some occasions a dominant gene may be responsible and in others a recessive gene Harris (1949) considers that it is unlikely that any very simple genetic formula can adequately account for all the observed phenomena

The matter becomes of importance when a young diabetic asks advice regarding marriage and the chances of begetting diabetic offspring In the light of our present knowledge it would seem that the marriage between two diabetics is likely to result in all their children being potential diabetics although they need not necessarily become frankly diabetic (In each group of 100 children from diabetic parents only 44 will actually develop the disease (Joslin 1952) The marriage in which one partner is diabetic and the other partner is not diabetic and has had no diabetic relatives is unlikely to bear diabetic children However these children will be capable of transmitting the disease but unless they marry partners who are also carriers their children will not become diabetic)

Race There is also a certain racial predisposition It is well recognized that the disease is particularly liable to affect Jews Rudy and Keeler (1939) investigated this subject and found that Jewish diabetics at all ages show a high incidence of the familial type of history and a higher incidence of the hereditary type at the younger ages

Intermarriage is doubtless an important factor in these observations but in addition the characteristic physique of the Jew tends towards endomorphy with its predisposition to obesity and this is one of the main precipitating factors in diabetes

The Chinese and Japanese have a low incidence of diabetes and this is also probably related to their natural dietary habits (Duncan 1952)

Nutritional State The nutritional standard of the population is also closely related to the incidence of diabetes and during both world wars when the nutritional standards fell to low levels in Germany the incidence of diabetes in that country was low Conversely it has been found that over

nutrition is associated with an increased incidence of the disease/ Himsworth (1949) drew attention to the falling death rate in England and Wales from diabetes since 1939 most likely due to a falling incidence of the disease during World War II This falling death rate occurred among the middle aged and elderly Common experience showed that during food rationing the majority of people in the country lost weight The association between diet and mortality could not be explained by the effect of diet on the survival of established cases of diabetes but by its effect on those persons who had not yet developed diabetes

ENDOCRINE FACTORS

As already indicated there are a number of endocrine dis orders which may be associated with diabetes and this applies in particular to diseases of the pituitary thyroid and adrenal cortex

Diabetes and the Pituitary

1 *Acromegaly* As already mentioned Cushing and Davidoff (1927) reported 100 cases of acromegaly in which glycosuria occurred The association between acromegaly and diabetes has since been stressed by many workers Coggeshall and Root (1940) reviewed 153 cases of acromegaly including the 100 reported by Cushing and Davidoff and found glycosuria in 36 per cent of the cases and frank dia betes in 17 per cent They found that the diabetes was usu ally diagnosed after the acromegaly with an average time interval of 9 2 years They suggested that diabetes is more likely to occur in acromegaly when there is a constitutional or hereditary predisposition because 21 per cent of the dia betic acromegalic patients had a family history of diabetes whereas among relatives of 127 acromegalics without dia betes only 2 per cent had diabetic relatives

The weight history of diabetics with acromegaly resembles that of the diabetic population in general in that 73 per cent of the acromegalics who became diabetic had previously been above their ideal weight

An amelioration in the diabetes in acromegaly has been

reported following the administration of large doses of oestrogen (McCullagh Beck and Schaffenburg 1955) In 5 cases these workers noted a reversal to normal or near normal glucose tolerance curves after such treatment and



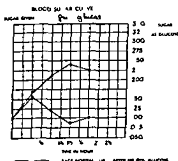


Fig III 2—Mrs A A *aet* 60 Acromegaly with diabetes (Dr Una Ledingham s case)

they suggested that the effect was due to the inhibition of the secretion of growth hormone by the anterior pituitary

Diabetes developing in a case of acromegaly is shown in Fig III 2

2 *Diabetes and Pituitary Insufficiency (Hypopituitarism)* The non diabetic who develops Simmonds's disease is abnormally sensitive to insulin Mogensen (1940) observed severe hypoglycaemic reactions in a woman aged 48 with Simmonds's disease the blood sugar falling to 38 mg per 100 ml Similarly the diabetic who develops pituitary insufficiency shows a marked amelioration of his diabetic state This was first demonstrated in the experimental animal by Houssay (1936) He found that the diabetes in dogs rendered diabetic by pancreatectomy became much less severe after hypophysectomy

Diabetes and the Thyroid Gland

1 *Hyperthyroidism* Allan *et al* (1947) found that diabetes is about twice as common in patients with thyrotoxicosis (2–4 per cent) as in the general population (1–2 per cent) The incidence of diabetes is greater in patients with toxic nodular goitre than in those with primary thyrotoxicosis This is probably related to the older age of the former group and to the fact that patients with primary thyrotoxicosis usually seek medical attention earlier so that there is more opportunity for precipitating diabetes in cases of toxic nodular goitre (Regan and Wilder 1940) When the two diseases are associated the thyrotoxicosis precedes the diabetes in 75 per cent of cases (Houssay 1946) The severity of the diabetes may be increased with the development of thyrotoxicosis and Scriver (1948) has shown that this may be associated with an increase in insulin resistance

Griffiths (1939) suggested that thyroxine resists the action of insulin both in the liver and in skeletal muscle When the thyrotoxicosis is controlled either by anti thyroid drugs alone or by preliminary control with anti thyroid drugs and subsequent partial thyroidectomy the diabetes becomes more readily controlled

2 *Myxoedema* This is uncommon in diabetes but when

it does occur there is usually an improvement in the diabetic state and in the case reported by Soffer (1956) there was a fall in the insulin requirement but after starting thyroid extract the dose returned to its former amount

Diabetes and the Suprarenal Cortex

1 *Cushing s Disease* Diabetes is frequently present in cases of Cushing s disease whether due to adrenal cortical hyperplasia or actual tumour formation Spence (1953) states that more than half such cases are diabetic but Lukens *et al* (1937) in a series of 55 cases found no impairment of *carbohydrate metabolism in 28 cases marked glycosuria in* 19 transitory glycosuria in 5 and a frank diabetic type of glucose tolerance test in the remaining 3 cases

Sprague *et al* (1943) reported a case in which the only manifestation of an adrenal cortical tumour was diabetes mellitus

The disturbance in carbohydrate metabolism is probably brought about in two ways Hyperfunction of the adrenal cortex influences protein metabolism with the result that there is an increase in gluconeogenesis Secondly certain of the adrenal cortical hormones have been found to decrease the rate of peripheral oxidation of glucose in the peripheral tissues

2 *Addison s Disease* Adrenocortical and islet cell insufficiency may become manifest simultaneously or either may precede the other Simpson (1949)

When a patient with diabetes develops Addison s disease the diabetes is modified considerably The hyperglycaemia and glycosuria are greatly reduced The insulin requirements fall and the patients become extremely sensitive to *insulin so that dangerous hypoglycaemia may occur* Soffer (1956) reported 50 cases in which diabetes and Addison s disease co existed 24 of the cases were collected from the world literature and 26 cases were observed by the author himself In *8 of these the two diseases presented together* in 5 the Addison s disease preceded the diabetes and in the remaining 13 cases the diabetes preceded the Addison s disease

In the differential diagnosis other causes of an increased

sensitivity to insulin such as hypopituitarism liver disease and hypothyroidism must be considered but when it has been established that the patient has both Addison s disease and diabetes each must be treated on its own merits with appropriate substitution therapy

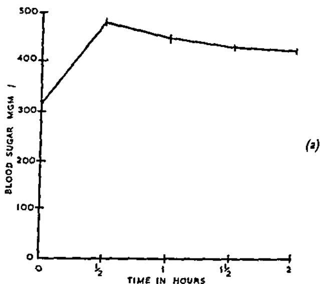
Pancreatic Disease

Primary pancreatic disease is only rarely the cause of diabetes Cases of acute pancreatitis are often associated with



FIG III 3 —Calcification of the pancreas in a young woman R H aged 21 with mild diabetes (Dr Ledingham s case)

glycosuria and hyperglycaemia In fulminating cases of this disease the outcome is often fatal so that the diabetes may only be of minor importance but in a few cases calcification of the pancreas may occur and a mild diabetic state results This occurred in a case of a young woman aged 21 who complained of recurrent upper abdominal pain and in whom calcification of the pancreas (see Fig III 3) and glycosuria were both discovered A glucose tolerance test revealed a mild diabetic state which was adequately controlled by diet alone



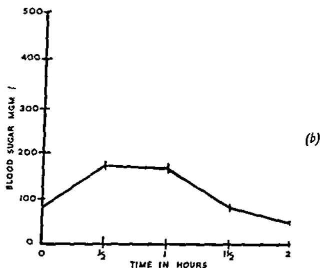


FIG III 4 —GLUCOSE TOLERANCE TEST
(a) At diagnosis of diabetes Wt 17 st (238 lb)
(b) One year later Wt 10 st (140 lb)

Carcinoma of the pancreas is not infrequently associated with mild diabetes and when treated by total pancreatectomy frank diabetes must inevitably develop Cutforth and Powell (1958) reported the development of diabetes in a patient with an oat celled bronchial carcinoma who developed metastases in the pancreas Sarcoidosis affecting the pancreas has also been thought to have been responsible for rendering the patient diabetic

Total pancreatectomy has been performed for carcinoma chronic pancreatitis hyperinsulinism and sarcoma The resulting diabetes is relatively mild with little tendency to spontaneous ketosis and coma The daily insulin requirement is usually 20–40 units The insulin requirement in a patient who is a known diabetic prior to total extirpation of the pancreas may be decreased unaltered or slightly increased following the operation Cattell and Warren (1953) Occasionally the altered sensitivity to insulin is a major problem and Ditun (1954) reports a case of a patient developing severe insulin resistance following pancreatectomy

Diabetes and Obesity

Obesity has long been recognized as one of the commonest of the conditions associated with diabetes and Joslin Dublin and Marks (1935) considered overweightness to be the chief constitutional factor predisposing to the onset of the diabetic state In particular it has been shown by Tyner (1933) that diabetes is more common in obese patients who have a family history of diabetes and Joslin (1952) found in reviewing 1 000 successive cases of diabetes that 77 per cent of these were above their standard weight zone

The recognition of obesity as a precipitating factor in diabetes is of great practical importance In many cases the mildly diabetic glucose tolerance curve of the obese patient can be restored to normal by weight reduction and carbohydrate restriction Newburgh and Conn (1939) found over 90 per cent of patients responded in this manner and also noted that recurrence of the obesity is capable of reproducing the hyperglycaemia and the delayed utilization of dextrose and that subsequent reduction of weight again corrects the

disturbance of carbohydrate metabolism However Richardson (1953) found that the glucose tolerance tests in a group of obese diabetics remained abnormal in the majority of cases Fig III 4 shows the glucose tolerance curves of a patient before and after weight reduction

The recognition of the importance of obesity in the aetiology of diabetes offers a *great opportunity for prophylactic* medicine The obese person with a diabetic relative should be advised against further weight gain and indeed encouraged to lose weight in order to forestall any tendency to develop frank diabetes

CONSTITUTION AND DIABETES

The precise aetiology of obesity remains unknown Newburgh *(1942) has emphasized that for a person to become* overweight he must at some time have eaten more than he needed to replace expended energy Certainly there are many persons who are overweight because they habitually *overeat—possibly as a result of an acquired habit* Nevertheless there is clearly a physical predisposition to obesity in certain persons and in view of the high incidence of diabetes as well as of hypertensive cardiovascular disease in patients *with obesity it is important to recognize any physical factors* predisposing to the development of obesity In this respect Sheldon s conception of the somatotype is of some assistance

Sheldon (1940 1954) has described physique as a mixture *of three inter related components called endomorphy* mesomorphy and ectomorphy Each component is exhibited in greater or lesser degree in all people The amount present is rated on a scale of 1–7 the somatotype being expressed as a *set of three ratings e g 3 4 3 The components* are most simply described by reference to individuals extreme in one of them and minimal in the other two The characteristic features of the extremes are shown in Fig III 5 which illus*trates patients included in a survey* carried out at the Royal Free Hospital (Lister and Tanner 1955)

The extreme in endomorphy approaches the spherical as near as is humanly possible he has a round head a large fat abdomen protruding beyond his thorax and weak penguin

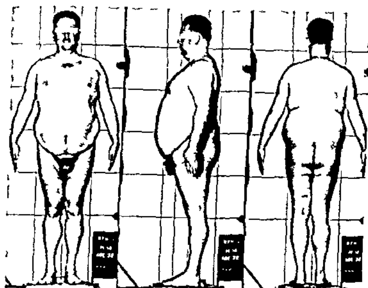
like arms and legs with a great deal of fat in the upper arm and thigh but slender wrists and ankles Relative to his general size he has a large liver and spleen and gut large lungs and a heart distinguishable in shape from the hearts of the other extremes When young the endomorph of rating 4 or even 5 might not be called frankly obese by the clinician but as he grows older his tendency to put on fat may bring him into this category

The extreme in mesomorphy is the classical Hercules in him bone and muscle predominate He has a cubical massive head broad shoulders and chest and heavily muscled arms and legs with the distal segments strong in relation to the proximal He has a minimal amount of subcutaneous fat and small anteroposterior diameters of the body

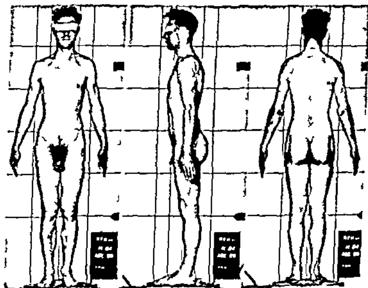
The extreme in ectomorphy is linear he has a thin peaked face with a receding chin and high forehead a thin narrow chest and abdomen a narrow heart and spindly arms and legs He has neither much muscle nor much subcutaneous fat but relative to his size he has a large skin area and a large nervous system

If this classification of physique is accepted it is clear that it is the person with a predominence of endomorphy who is predisposed to obesity On carrying out an anthropological study of a group of diabetic patients at the Royal Free Hospital (Lister and Tanner 1955) there was no doubt that a large number of the patients were high in endomorphy Furthermore it was largely possible to relate the clinical type of diabetes to the patient s physique The patients were divided into two clinical groups those with an acute onset and those with a non acute onset of their diabetes Those patients whose diabetes came on insidiously were more endomorphic than those who developed acute diabetes usually at an earlier age

Similar observations on the physique of diabetics have been made by other workers Draper *et al* (1944) found they could divide their diabetics into two clear morphological groups—linear and rounded The linear patients usually had severe diabetes of acute onset and had become ketosed with poor control and the rounded ones had less severe

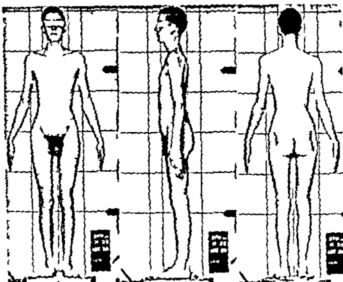


(a)



(b)

FIG III 5—Constitutional types in diabetes The extremes of (a) endomorphy (b) mesomorphy and (c) ectomorphy



(*Illustrations reproduced by courtesy of the Editor of the Lancet*)

(c)

diabetes of insidious onset and with little tendency to ketosis and hypoglycaemia. These are of course the two clinical groups of patients so well recognized by all interested in diabetes the former being the group whom Himsworth (1949) found insulin sensitive and the latter insulin insensitive. Lawrence (1951) has emphasized that the first group are clinically insulin deficient and the second group which he describes as lipoplethoric are clinically not deficient in insulin. Estimation of plasma insulin by Bornstein's technique tended to confirm these observations (Bornstein and Lawrence 1951).

The somatotype by definition does not change with age but the body contour does and more in endomorphs than in others. The amount of fat a person puts on as he gets older depends on his degree of endomorphy (see the standard age weight curves for various somatotypes in Sheldon 1954) and it has been very tentatively suggested that the reason for this may be that the endomorph has more fat cells than have

the others just as the mesomorph has more muscle cells (Tanner 1955) Thus persons high in endomorphy run various special risks as they grow older some by virtue of the tendency of their fat cells to fill up One of these risks seems to be that of developing non acute extrapancreatic lipoplethoric diabetes

On the other hand the acceptance of the suggestion that persons high in endomorphy are liable to become obese may go a long way to explaining the racial and familial predisposition to diabetes—especially of the mild type of insidious onset—and it is suggested that the recognition of endomorphy as a predisposing factor in diabetes is of considerable importance from the aspect of preventive medicine ( )

Precipitating Factors In considering the question of precipitating factors in diabetes it is important to accept the principle that persons who become diabetic have probably been potentially diabetic from birth and that they have an inherently deficient pancreatic islet cell reserve (Wilder 1950) It is probable that some factor may be required to precipitate a final breakdown in carbohydrate metabolism and although it may not always be possible to determine the nature of this factor there are certain well recognized associations Thus obesity as already stressed is the commonest predisposing factor while such endocrine disturbances as acromegaly thyrotoxicosis Cushing s disease and pregnancy may be sufficient to disturb the endocrine balance Similarly a number of cases become manifest at the menopause while infections such as boils and carbuncles may cause latent diabetes to become manifest

As with so many other diseases when a patient is told he has diabetes he immediately tries to find some contributory cause Notoriously he seeks a history of trauma of one kind or another in order to explain his disease Most authorities discard trauma as having any direct aetiological bearing on the development of diabetes although it is conceded that latent diabetes may become manifest after certain traumatic experiences Investigating the effect of direct trauma upon carbohydrate metabolism Thomsen (1938) studied the blood and urine of 144 patients at the time of and subsequent to

accidents He found no essential difference between the injured and non injured persons

In a personal series of 300 cases in which the onset of the disease was studied 19 per cent of the patients stated that they related the onset of their symptoms to psychological factors The majority were vague about their nature and simply described how they had been subjected to a long period of nervous strain Others mentioned the close relationship between specific war time bombing incidents and the onset of symptoms and others claimed the deaths of relatives as important factors In one case a land mine falling in the back garden and in another the finding of a near relative dead in bed were closely followed by thirst and polyuria The most remarkable history was given by a child of eleven years who first developed diabetes at the age of three When asked if he remembered how his illness started he described in detail how a visiting circus came to his village and how he suffered a severe shock when one of the horses broke loose and charged in his parents front garden and smashed a window of the house Shortly afterwards he developed acute diabetic symptoms The incident no doubt made a great impression on the child but it was presumably the unconscious wish of the parents to find some tangible cause for the child s illness which made them associate the episode with the onset of diabetes

The possibility of mental or physical trauma being a precipitating cause of diabetes has naturally led to claims for disability pensions particularly in Service personnel Although the claims are often rejected it does appear that others have been admitted Vatcher (1935) in discussing the aetiology of diabetes in war pensioners considered that the nervous stress and strain to which the men were continually subjected during war service was a potent factor in determining the onset of diabetes Many of these cases from World War I and others from World War II are still under observation at the Ministry of Health Hospital at Roehampton (Vatcher 1937)

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CHAPTER IV

PRESENTATION AND DIAGNOSIS

THE PRESENTATION

THE frank diabetic symptoms of thirst, polyuria and weight loss are only present when there is an absolute deficiency of available endogenous insulin This occurs when total pancreatectomy is performed when the islet cells are destroyed by injections of alloxan (Dunn *et al* 1943) and in severe cases of diabetes mellitus In these circumstances there is a break down in the physiological processes which normally occur under the influence of insulin and hyperglycaemia results When the blood sugar level rises above the renal threshold for sugar glycosuria results with an increase in the osmotic pressure of the glomerular filtrate and a consequent reduction in the renal tubular reabsorption and hence polyuria This in turn is responsible for the extreme thirst of the severe case in which a greater or lesser degree of dehydration occurs and is the major cause of the rapid weight loss The other factor in the weight loss occurs when there is an extreme deficiency of insulin and the energy requirements of the body can no longer be met from glucose and an excessive breakdown of body fat occurs In these cases there is ketonuria in addition to glycosuria and if the process is allowed to proceed unchecked there is an increasing ketosis and the symptoms of diabetic pre coma will eventually appear In the majority of patients however the insulin deficiency is not severe enough to cause such dramatic symptoms and the presentation is often indefinite and the time of onset difficult to determine

In children it is occasionally the case that a specific day or even a specific hour can be recalled as the time when thirst and polyuria abruptly began Young adults can often narrow the onset of the symptoms down to a week or a month but in many cases the symptoms have begun so insidiously that the patients cannot recall when they first started with

any degree of accuracy Indeed the discovery of glycosuria is often made on routine urine examinations and the presence of any diabetic symptoms is stoutly denied It is in this group of patients that it is impossible to determine how long carbohydrate metabolism has been disordered although when such patients are found to have retinopathy or albuminuria with oedema this has been accepted as evidence that hyperglycaemia has existed for upwards of ten years

Type of Onset

1 **The Acute Onset** Typically this presentation is seen in the young patient who is usually not overweight and in whom the disease is severe It may however occur at any age even in the elderly in whom diabetes has often been described quite erroneously as being a mild condition There is usually a severe insulin deficiency and it is urgent to institute treatment with carbohydrate restriction and insulin If such treatment is delayed the symptoms will become rapidly more severe and the case will progress to ketosis with the dangers of diabetic pre coma or coma Indeed it is among patients with such an onset that diabetic coma may be the presenting feature

2 **The Non acute Onset** Many diabetic patients present with a more insidious onset of diabetic symptoms only leading to diagnosis after months or even years Although this type of presentation may occur whenever there is a mild degree of insulin deficiency it is most characteristic of the middle aged obese female diabetic In this group of patients pruritus vulvae is the commonest presenting symptom

3 **Presentation with Diabetic Complications** The diagnosis of diabetes mellitus is often not made until the patient has developed either a condition which may be regarded as a complication of diabetes or develops a condition so often associated with diabetes that a urine examination for sugar is always carried out in its presence

The commonest conditions in this group are

(a) Superficial sepsis—especially boils and carbuncles and occasionally iritis—or other forms of uveitis
(b) Failing vision due to cataract or diabetic retinopathy

(c) Peripheral vascular disease causing intermittent claudication or ischaemic types of gangrene

(d) Diabetic neuropathy in any of its several forms

(e) Diabetic nephropathy with oedema and albuminuria

(f) Occasionally patients with cardiac infarction or hypertension are found to be diabetic on routine urinalysis

(g) The investigation of obesity may include a glucose tolerance test and some degree of carbohydrate intolerance is found in a proportion of cases

4 **Diagnosis on Routine Urinalysis** Glycosuria may be discovered on routine urine examination when there is no clinical suspicion of diabetes and when the patient admits no diabetic symptoms

The common circumstances of such examinations are life insurance and National Service medical examinations routine urine examination carried out pre operatively and in ante natal clinics—or even in post natal clinics especially after a stillbirth

5 **Presentation with Associated Endocrine Disorder** In a small number of cases glycosuria may be discovered during the investigation of an endocrine disturbance such as thyrotoxicosis acromegaly or Cushing s syndrome

Frequency of Symptoms

Although it is clear from the foregoing that many patients may have no diabetic symptoms at the time of diagnosis it is worth analysing the frequency of the more common symptoms From a survey carried out in the diabetic clinic at the Royal Free Hospital the symptoms admitted at the time of diagnosis in 578 patients are shown in Fig IV 1

Thirst Polyuria Weight Loss These are the classical symptoms of acute insulin deficient diabetes They occur with almost equal frequency and nearly always in association with each other Many diabetics do not distinguish true polyuria from increased frequency of micturition The two symptoms of course occur frequently together the former causing the latter On the other hand it is sometimes suggested that many diabetics do not have true polyuria but

suffer increased frequency due to irritation of the bladder by the high sugar content of the urine

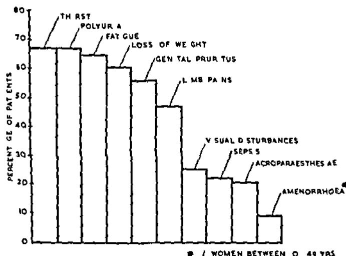
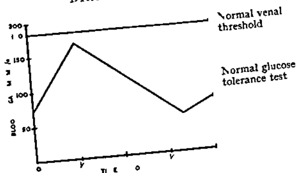
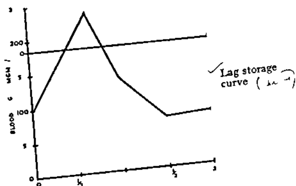


FIG IV 1 Incidence of the common symptoms present at time of diagnosis (578 patients at Royal Free Hospital)

Genital Pruritus This is the commonest symptom in women with an insidious onset of diabetes In mild cases the glycosuria may at first be intermittent and in unexplained cases of pruritus vulvae an examination of the urine for sugar should be made on every attendance and in doubtful cases a glucose tolerance test should be carried out In particular it should be emphasized that the early morning urine specimens may be sugar free whereas post prandial specimens reveal glycosuria

Visual Disturbances In the series of 578 patients visual disturbances were present in 132 patients Transient blurring of vision without any occular abnormality and usually with improvement after the control of the diabetes was the commonest finding being present in 71 2 per cent of the cases It was an especially common symptom in patients with an acute onset Cataract was present in 29 patients and diabetic retinopathy in 11


venal threshold
Normal glucose tolerance test
200
150
100
50
BLOOD
0


Lag storage curve
200
100
BLOOD
0
½

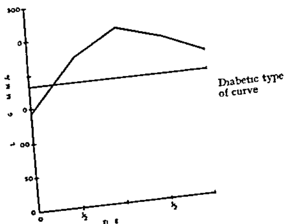

Diabetic type of curve
300
50
0
½

FIG. IV 2

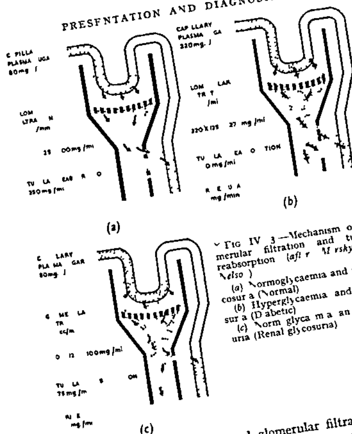


FIG IV 3.—Mechanism of glomerular filtration and tubular reabsorption (after Mirsky and Nelson)

(a) Normoglycaemia and no glycosuria (Normal)

(b) Hyperglycaemia and glycosuria (Diabetic)

(c) Normoglycaemia and glycosuria (Renal glycosuria)

other cases he found a lowered glomerular filtration rate resulting in a decreased load In each case the result was a raising of the renal threshold for sugar Conversely the threshold may be lowered and so-called renal glycosuria result when there is either a diminished tubular reabsorption or an increase in the glomerular filtration rate Mirsky and Nelson (1943) and Corcoran (1948) have found that in symptomless renal glycosuria there is usually normal glomerular function but an impaired renal reabsorptive mechanism (See Fig IV 3) Clinically the diagnosis of a lowered renal threshold may be made when there is glycosuria with normoglycaemia. There is no known relationship between lowering of the renal

threshold and diabetes but the two conditions can occur simultaneously Downie (1952) Wilder (1940) Lawrence (1955) When they do so the management of the diabetic is made more difficult and blood sugar estimations rather than urine sugar estimations have to be the basis for control In the diabetic it is often difficult in clinical practice to determine accurately the renal threshold and it can only be done by relating frequent blood sugar estimations to the glucose content of urine specimens secreted and collected over the same period of time

Renal Threshold in Pregnancy In pregnancy the renal threshold is temporarily lowered and Williams and Wills (1929) found symptomless glycosuria in 5 4 per cent of 640 unselected pregnant women In a proportion of such cases a glucose tolerance test will reveal a diabetic curve but in others a normal curve with a lowered renal threshold is discovered *In the latter instance no special treatment apart* from spacing carbohydrate meals is required but the lowering of the renal threshold in pregnancy in diabetics complicates the management of the pregnant diabetic woman (p 178)

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CHAPTER V

STABILIZATION OF THE DIABETIC

Introduction Since the discovery of insulin by Banting and Best (1922) the expectation of life for the diabetic has been greatly extended and it should now be rare for a diabetic to die in diabetic coma. On the other hand the increased longevity has shown that after 15 or 20 years of diabetes the incidence of serious diabetic vascular disease is alarmingly high especially amongst those who develop diabetes in early life. This problem provides the greatest challenge to modern methods of treatment of diabetes. There are those who insist that the maintenance of strict diabetic control is the best way of avoiding complications (Joslin 1952) while others notably Lister and Weber (1939, 1940) believe that there is insufficient evidence that hyperglycaemia *per se* is sufficiently harmful to justify this rigid discipline of a patient's life which such control demand. Nevertheless it has been stressed by Lukens (1950) that hyperglycaemia is a sign of uncontrolled diabetes and that uncontrolled diabetes certainly produce some damaging agents as shown by the frequency of complications. Until more is known about what must be controlled to avert these complications it seems proper to keep the diabetic as nearly physiologically normal as possible by all available criteria.

Assuming that in the present state of our knowledge this is an acceptable hypothesis, the aims of treatment may be summarized as follows:

(1) The elimination of all symptoms of diabetes (in particular thirst, polyuria and nocturia).
(2) The strict avoidance of ketonuria.
(3) The maintenance of blood sugar levels as nearly within the normoglycaemic range as possible.
(4) The avoidance of hypoglycaemic reactions.

(5) The maintenance of the patient within his optimum weight range—with particular emphasis on the importance of weight reduction in the obese

(6) The restoration of the patient to a position of social and economic usefulness

The measures required to fulfil these aims of treatment depend upon the clinical features of the case It is now recognized that hyperglycaemia and glycosuria are the result of either an absolute or a relative deficiency of available insulin (Long 1942) In the treatment of both types of case some restriction of carbohydrate is necessary but it is only when there is an absolute insulin deficiency that replacement therapy is necessarily required

Before considering the detailed treatment of the various clinical types of the disease it is well to review the ways in which diabetes can be produced experimentally and to see what analogies can be drawn with the types encountered in man

1 **Diabetes Due to Absolute Insulin Deficiency (Pancreatic Diabetes)** The most characteristic diabetes is produced by pancreatectomy as was performed by Von Mering and Minkowski (1889) in dogs These animals developed acute thirst and polyuria lost weight became ketotic and finally died in diabetic coma Alloxan injections have been shown to destroy islet cell tissue with resultant diabetes of similar type (Dunn *et al* 1943) The cause of the diabetes in such cases is clearly an absolute deficiency of insulin An exactly analogous type of diabetes can be produced in man when total pancreatectomy is performed for carcinoma of the pancreas (Ricketts *et al* 1945) Less severe diabetes may occur when some of the islet cell tissue is involved in carcinoma of the pancreas and in cases of pancreatitis—especially when calcification takes place

The spontaneous type of diabetes with an acute onset with severe symptoms of thirst polyuria and weight loss and carrying the danger of ketosis and coma is regarded as being due to an absolute deficiency of insulin It is the type which almost invariably occurs in the juvenile usually occurs in the young adult and not infrequently occurs in the elderly Be

cause the deficiency of insulin is absolute replacement therapy is always required in addition to restriction of carbohydrate intake

2 **Diabetes Due to Relative Insulin Deficiency (Extra pancreatic Diabetes)** Wilder (1950) maintains that a healthy endocrine gland should have such reserves that it can secrete adequate hormone to meet any demand made upon it and that failure to do so is an indication of a deficient reserve Applying this principle to diabetes he believes that in some cases diabetes occurs because of an abnormal demand for insulin or because of the presence of insulin antagonists The nature of the latter is poorly understood and indeed the exact mode of insulin action is still not known but there is no doubt that the control of carbohydrate metabolism involves a number of complex hormonal interrelationships and as already mentioned diabetes is not infrequently met in association with other endocrine dis orders *In particular* it has long been recognized that diabetes is frequently present *in* acromegaly in Cushing s syndrome and in thyrotoxicosis In these cases it may well be that a relative insulin deficiency is conditioned by complex hormonal activity which either interferes with insulin action or causes an increased insulin demand. Correction of the overt *endocrine disturbance* often results in a recovery of normal carbohydrate tolerance Far commoner however than the relationship between diabetes and other frank endocrine disorders is the relationship between diabetes and obesity According to Long (195-) the storage of fat requires the presence of insulin and obesity probably results *in* an extra insulin demand It is suggested therefore that the type of diabetes which develops gradually and characteristically occurs in obese *middle* aged persons is probably due to a relative deficiency of insulin *conditioned* by the obesity There is probably an inherited tendency towards such diabetes In these patients dietary measures aimed at weight reduction and carbohydrate restriction may so relieve the pancreatic islet cell load that the relative deficiency of insulin disappears Insulin therapy may be required in the early stages of treatment but *it is* often possible to

avoid it altogether and permanent insulin therapy in these cases has the disadvantage of encouraging further weight gain

In clinical practice the two types of diabetic patient which have now become quite clearly recognized are firstly those with an acute onset of diabetic symptoms and who will eventually become ketotic and pass into diabetic coma if not treated and secondly those with a more gradual onset of symptoms and who rarely develop ketosis

The first type of diabetes can occur at any time of life but is usually most severe in the young The patients are rarely frankly obese but careful history taking will often reveal that the patient s maximum weight has been reached just prior to the onset of the diabetic symptoms The second type occurs most characteristically in obese middle aged persons and more often affects women than men

Both types of case require dietetic treatment those cases with acute symptoms indicating an absolute insulin deficiency will almost invariably require insulin therapy In the mild obese type of case every effort should be made to control the condition by diet alone

Dietetic Treatment

In all cases of diabetes it is necessary to restrict carbohydrate intake Most authorities now allow a free protein intake because although there is some conversion of protein to glucose it has been found that the diabetic person s sense of well being is enhanced by a generous protein intake (Duncan 1951)

In prescribing a diet it is also important to consider the total calorie intake with due regard to the patient s age sex weight and occupation In particular in the obese patient the total calorie intake must be restricted to about 1 000 C and the fat content should be kept low (approximately 50 G daily) It is wise to aim at maintaining the patient just below the optimum weight Quite apart from advising the patient on his total calorie intake he should be advised to try to be constant in his dietary habit from one day to the next as this is of great benefit in maintaining good diabetic con

trol Those who advocate a free diet hold that most persons are in fact relatively constant in what they eat each day and believe that for this reason it is possible and desirable to prescribe the amount of insulin found necessary to control *hyperglycaemia and glycosuria on the patient's own choice* of diet—the only condition being that he remains rigidly on the diet Unfortunately such a diet may be too generous both in carbohydrate and total calorie content with the result that the insulin promotes further weight gain

The chance of a patient remaining strictly on the diet advised depends largely upon its being simple and dogmatic The daily amount of carbohydrate should first be ordered but *each case has to be individually considered and there* can be no firm rules

The following figures may be taken as a guide

The obese patient requires	100–120 G Carbohydrate a day
The average weight sedentary worker	150–200 G Carbohydrate a day
The worker in heavy *industry*	*200–250 G Carbohydrate a day*

Children and adolescents require a diet relatively high both in calories and carbohydrates

In patients taking no insulin the diet can be spread evenly through the day but persons on insulin require the diet to be distributed with due regard to the duration of action of the insulin preparation being used (see Table 9) Thus adequate carbohydrate must be given to cover the maximum effect of *the insulin and to counteract any hypoglycaemic effects The* physician must also be prepared to re arrange the distribution of carbohydrate to suit individual needs as in the case of travellers and those having to undertake shift work

Many diet sheets and forms have been devised for diabetics and the best known is the Line Ration scheme prepared by Dr Lawrence Each black line describes amounts of foods which contain 10 G carbohydrate so that the diet *may easily be prescribed in terms of lines* but it is now more general to refer to 5 gm portions Other workers prefer to prescribe the diet in terms of a total daily allowance of

carbohydrate and space it throughout the day in such a way as it will meet the wish of the patient as far as possible and at the same time be satisfactory from the point of view of diabetic control

It is important that the doctor in charge of the case should have a working knowledge of the carbohydrate content of the commonly used carbohydrate foods and that the patient should also understand the principles of his dietetic treatment It is a great advantage to have the assistance of a trained dietician in the management of diabetics but it does not relieve the physician of being able to prescribe the diet himself Whatever form of dietary prescription sheet is actually used every diabetic patient should be provided with information regarding the carbohydrate content of different foods First there should be a list of those foods containing no more than a negligible amount of carbohydrate of which he is free to partake according to his appetite (see Table 1) and another general list of carbohydrate foods which may only be taken in stated amounts according to the diet prescribed (see Table 2) There should follow a more detailed complementary list giving the amounts of the food stuffs which contain 5 G of carbohydrate this amount commonly being described as one portion (see Table 3)

Table 1 Foods of Negligible Carbohydrate Content which may be taken according to Appetite

Protein or Fat Foods (Not to be taken freely if weight reducing) Meat bacon offal fish rabbit poultry game Butter margarine fats cheese

Vegetables Green artichokes asparagus scarlet runner and French beans broccoli Brussels sprouts cabbage cauliflower celery chicory cucumber greens horse radish leeks lettuce mushrooms mustard and cress onions for flavouring parsley radishes seakale spinach tomatoes turnips watercress

Fruit and Conserves Stewed blackberries cranberries loganberries stewing gooseberries grapefruit lemons and lemon juice rhubarb diabetic jam and marmalade

Condiments and Flavourings Salt pepper mustard vinegar curry powder unsweetened pickles herbs saccharine vanilla gelatine lemon rice and peel orange peel

Beverages and Soups Tea coffee water soda water diabetic fruit drinks clear soups Marmite Oxo Bovril

Table 2 CARBOHYDRATE FOODS WHICH MAY ONLY BE TAKEN IN STATED AMOUNTS

Sugar glucose syrup jam marmalade honey sweets chocolate ice cream
Milk and milk beverages e g Horlicks Ovaltine
Flour and all foods cooked with flour e g pastry Yorkshire pudding suet crust stuffing buns cakes biscuits thick soups sauces and gravies
Oatmeal barley pudding cereal breakfast cereals
Bread
Potatoes parsnips lentils peas and beans (except scarlet runner and French)
Chestnuts and peanuts
Fruit (except those on free list)

Table 3[1]

Foods in amounts containing 5 G carbohydrate (often described as 1 portion)

1 Cereal Foods

Although the carbohydrate content of pudding cereals does vary as in the following lists for simplicity it is reasonable to consider that ¼ oz pudding cereal contain 5 G carbohydrate

Food	*Description*	*ozs*	*G CHO per oz*
Bread	White before toasting	⅓	15 2
	Wholemeal before toasting	¼	12 4
Breakfast cereals all kinds (oatmeal cornflakes etc)		¼	
Cornflour		¼	26 1
Custard Powder		¼	26 1
Flour	White	¼	22 7
	Wholemeal	¼	10 0
Macaroni	Raw	¼	21 8
Rice	Raw	¼	24 6
Sago	Raw	¼	26 [illegible]
Semolina	Raw	¼	2
Biscuits	Plain mixed	¼	21 4
	Cream Crackers	¼	16 3
	M tras	¼	
	Vitawheat	¼	19 4
	Ryvita	¼	22 4

[1] The quantities were calculated from figures taken from McCance R A & Widdowson E M (1951) *The Chemical Composition of Foods* Medical Research Council Special Report Series No 235

2 Milk and Milk Beverages

Food	*Description*	*o s*	*G CHO per oz*
Fresh	Whole	3½	1 3
	Skimmed	3½	1 4
Condensed	Unsweetened	1½	3 3
Dried		½	10 4
Bengers food	Powder	1	
Bournvita	Powder	¼	19 2
Cocoa	Powder	½	9 9
Horlicks Malted Milk	Powder	¼	0 1
Ovaltine	Powder	¼	17 5

3 Vegetables

Food	*Description*	*o s*	*G CHO per oz*
Beans	Baked tinned	1	4 9
	Broad boiled	2½	[illegible] 0
	Butter Raw	½	14 2
	Butter Boiled	1	4·9
	Haricot Raw	½	1 ·9
	Haricot boiled	1	4 7
Beetroot	Boiled	1¾	2 8
Carrots	Boiled	4	1 [illegible]
Lentils	Boiled	1	5 2
Onions	Fried	1¾	2 9
	Spring raw	2	2 4
Parsnips	Boiled	1½	3 8
Peas	Fresh boiled	2¼	2 2
	Dried raw	½	14 2
	Dried boiled	1½	5 4
	Tinned	1	4 7
Potatoes	Boiled	1	5 6
	Chips	½	10 6
	Baked in skin pulp only	⅝	7 1
	Roast	⅝	7 8
Swedes	Boiled	4½	1 1

4 Fruit Fruit Drinks and Concentrates

Although the carbohydrate content of fruits does vary as in the following list for simplicity it is reasonable to consider that 2 ozs of most raw fruits contain 5 G carbohydrate The most notable exceptions are grapes and bananas of which 1 oz of the raw fruit contains 5 G

Food	*Description*	*o s*	*G CHO per o*
Apples	Raw with skin and core	2	2 6
	Stewed without sugar	4	1 2
Apricots	Fresh with stones	3	1 7
	Dried stewed without sugar	1	5 1
Bananas	Edible part	1	5 5

Food	*Description*	*ozs*	*G CHO per oz*
Blackberries	Raw	2¾	1·8
Cherries	Raw with stones	1¾	3·4
	With stones stewed without sugar	4	1·2
Currants	Black raw	2½	1·9
	Black stewed without sugar	4	1·3
	Black puree	½	
	Syrup	½	
	Dried	½	18
Damsons	Raw with stones		2·4
	Stewed with stones	2½	1·8
Dates	Dried	½	18·1
Figs	*Green raw*	2	2·7
	Dried raw	½	15·0
	Dried stewed without sugar	¾	8·5
Gooseberries	Raw ripe	2	2·6
Grapes	Black raw whole	1	3·7
	White raw whole	1	4·7
Greengages	Raw with stones	1½	3·2
	Stewed with stones without sugar	2½	2·2
Melon	Edible part	3½	1·4
Mulberries	Raw		2·3
Nectarines	*With stones*	1½	3·2
Orange	Edible part	2	2·4
	Juice	2	2·7
	Concentrated juice	½	
Peaches	Fresh with stones	2½	2·3
	Raw dried	½	15·0
	Dried stewed without sugar	1	5·1
	Tinned in syrup	1	4·9
Pears	Raw with skin and core	2½	2·2
	Stewed without sugar	2¾	1·8
	Tinned in syrup	1	4·7
Pineapple	Fresh edible part	1½	3·3
	Tinned in syrup	1	4·7
Plums	Victoria dessert with stone	2	2·6
	Stewing variety with *stones*	4½	1·1
Prunes	Dried raw with stones	½	9·5
	Stewed without sugar with stones	1	4·4
Raisins	Dried	½	18·3
Raspberries	Raw	3	1·0
	Stewed without sugar	4½	1·1
Rose hip syrup		½	

5 Miscellaneous Foods

Food	*Description*	*o s*	*G CHO per oz*
Strawberries	Fresh	2¾	1 8
Sultanas	Dried	¼	18 4
Tangerines	With peel and pips	3	1 6
Honey	In jars	¼	21 7
Jam		¼	19 6
Lemon Curd		½	11 4
Marmalade		¼	19 8
Mincemeat		¾	7
Sryup		¼	22 4
Treacle		¼	19 1
Jelly	In packet	¼	17 7
Icecream	Plain	1	5·0
Chocolate	Milk	⅓	14·9
	Plain	⅓	16 6
Sugar	White	⅙	28 4
Nuts	Peanuts weighed with shells	3	1 7
	Peanuts without shells	2	2 4
	Chestnuts weighed with shells	½	8 6

It is for the physician to decide upon the total carbohydrate content of each patient s diet and how it is to be spaced through the day and it is for the dietitian or the physician himself to advise the patient how he may obtain a reasonably balanced and varied diet by reference to the appropriate lists of foods he is allowed to take freely and by reference to the 5 G exchange lists of carbohydrate foods Patients also find it helpful to know the amount of other carbohydrate foods which may be exchanged for one ounce of bread as shown in Table 4

Table 4

Substitutes for 1 *o bread* (15 G = 1 slice ½ inch thick from small loaf)

- 2 Ryvita
- Vita wheat
- 3 Water biscuits
- 3 oz potatoes (boiled)
- ¾ oz breakfast cereal
- 3 oz stewed prunes
- ¾ oz Bournvita Ovaltine or Horlicks powder
- 1½ oz Cocoa
- ½ pint beer
- 1 oz chocolate

The degree of accuracy with which a patient actually follows his diet is difficult to assess but as patients become more

experienced in handling their diets they become proficient at judging weights and amounts of foods without actually using scales although in the early stage of educating the patient into proper diabetic dietary habits it is desirable to advise the use of diabetic scales

The more enthusiastic diabetic cooks will find many varied recipes which are suitable for the diabetic in a number of diabetic cookery books [1]

Table 5 EXAMPLE OF SUGGESTED MENU

Total Carbohydrate 150 G (Portions 30)

Meal	*To a Portions*	*Examples*	*Portions*	*Carbohydrate in G*
BREAKFAST	8	½ oz Cereal	2	10
		(Bacon egg or fish)		
		1½ oz bread	5	25
		3½ oz milk	1	5
MID MORNING	2	Tea or coffee		
		3½ oz milk	1	5
		Plain buiscuit	1	5
LUNCH	6	Meat fish or poultry		
		Unthickened gravy		
		4 oz potatoes	4	20
		4 oz carrots	1	5
		4 oz stewed apple	1	5
TEA	4	Tea		
		3½ oz milk	1	5
		1 oz bread	3	15
		Salad		
DINNER	8	Meat fish cheese egg		
		1 oz bread		
		Mild pudding		
		¼ pt milk	2	10
		½ oz cereal	2	10
		2 oz raw fruit	1	5
BED TIME	2	½ oz Ovaltine	1	5
		3½ oz Milk	1	5

[1] e.g. *The Complete Cookery Book for Diabetics* by I. Rogers published by H. K. Lewis & Co. for the British Diabetic Association

Table 6 REDUCING DIET

1 000 Calories Approximately

		FOOD VALUE		
		Carbohydrate gm	*Protein gm*	*Fat gm*
DAILY	Milk (½ pint)	14 0	10·0	11·0
	Margarine or butter (¾ oz)	—	—	18 0
BREAKFAST	Milk from daily ration in tea or coffee	—	—	—
	1 slice of bread (½ in slice from small loaf)	15 0	2 4	0 3
	Butter from ration	—	—	—
	1 egg or lean ham or piece of fish (not fried) or lean grilled bacon	—	7 0	7 0
MID MORNING	Marmite or tea or Oxo or Bovril	—	—	—
DINNER	Lean meat or fish or rabbit or tripe	—	14 0	10 0
	Large helping of green vegetables or salad	—	—	—
	Helping of fruit raw or stewed (no sugar)	10 0	—	—
TEA	Milk from ration in tea (no sugar)	—	—	—
	Salad if desired	—	—	—
	Bread 1½ thin slices and butter from ration	22 5	3 6	0 5
	Marmite meat or fish paste	—	—	—
SUPPER	Steamed fish or egg or lean meat or cheese (small helping)	—	7 0	5 0
	1 thin slice of bread or 2 very small potatoes	15·0	2 6	0 3
	Butter from ration	—	—	—
	Green vegetables or salad	—	—	—
	Fruit as at dinner OR ½ thin slice bread	10 0	—	—
	Calories 978	86 5	46 6	50 5

Each diabetic patient should have his own diet sheet and suggested menu which he is free to vary by the use of his exchange lists Each individual physician or dietitian tends to have *his own preferred method of prescribing the diet but* a suggested form is shown in Table 5 where the total carbohydrate value is shown together with the spacing throughout the day both in terms of portions and total carbohydrate to be taken at each meal

Weight Reducing Diets

In the obese case when weight reduction is essential the calorie content of food must be considered and in particular carbohydrates and fat must be restricted In these cases it is convenient to prescribe a 1,000 C diet with the approximate distribution of 85 G carbohydrate 45 G protein and 50 C fat as suggested in the diet sheet shown in Table 6 Tables 6*a* and *b* give the ideal weight charts for men and women

Table 6a Ideal Weights for Men*

Height (with shoes on) ft in	*Small frame*	*Medium frame*	*Large frame*
5 2	111–125	124 133	131–132
5 3	119–128	127–136	133 144
5 4	122 132	130–140	137–149
5 5	126–136	134 144	141 153
5 6	129–139	137–147	145 157
5 7	133–143	141 151	149–162
5 8	136–147	145–156	153 166
5 9	140–151	149–160	157–170
5 10	144–155	153 164	161 175
5 11	148–153	157–168	165–180
6 0	15 –164	161 173	169–185
6 1	157 169	166–178	174–190
6 2	163–175	171 184	179–196
6 3	168–180	176–189	184– 02

Weight in pounds according to frame as ordinarily dressed

* From Metropol tan L fe In rance Comap y
Ideal weights for men Metrop l ta Life I s Bull 24 6 1943

Alcoholic Beverages Unless there is evidence of liver damage there is usually no need to advise diabetics to abstain from taking alcohol in reasonable amounts and Table 8 (after Lawrence 1955) summarizes the carbohydrate content of the commoner alcoholic drinks

The following examples may help to illustrate some of the points described above

1 Housewife age 28 wt 126 lb
Insulin—Lente
Total daily Carbohydrate allowed—150 G

	G CHO	Portions
Breakfast	35	7
Mid morning	15	3
Lunch	35	7
Tea	25	5
Dinner	30	6
Bed time	10	2

2 Labourer age 32 wt 196 lb
Insulin—Lente
Total Daily Carbohydrate allowed—200 G

	G CHO	Portions
Breakfast	45	9
Mid morning	20	4
Lunch	45	9
Tea	25	5
Dinner	45	9
Bed time	20	4

3 Schoolboy Age 10 wt 100 lb
Insulin—2 doses soluble
Total Daily Carbohydrate allowed—180 G

	G CHO	Portions
Breakfast	50	10
Mid morning	20	4
Dinner	40	8
Tea	50	10
Bed time	20	4

4 Housewife Age 58 wt 180 lb
No insulin
Total Daily carbohydrate allowed—100 G

	G CHO	Portions
Breakfast	20	4
Mid morning	10	2
Lunch	20	4
Tea	15	3
Dinner	0	4
Bed time	15	3

Insulin Treatment

Seven Insulin Preparations Ever since insulin was isolated research has been carried on to produce an ideal preparation for exogenous administration Such a preparation should be depot in type and should release insulin as tissue sugar rises and withold it as tissue sugar falls thereby controlling hyperglycaemia and preventing hypoglycaemia Were such a preparation available it would be a complete replacement for normally functioning pancreatic islet cells and it is not surprising that it has not yet been found It is the persistent search for such a preparation which has resulted in the numerous preparations which are available today and it is confusing for the clinician that there are now no less than seven insulins on the British market (Table 9) It was the short action of soluble insulin (maximum duration of effect 6 8 hours) which stimulated the search for long acting preparations Soon after the discovery of insulin the Toronto workers found that various metals were important in the formation of insulin crystals and that certain proteins could prolong insulin action In particular it was found that the effect of protamine insulin one of the early retard insulins was substantially protracted by the addition of small quantities of zinc This observation led to the introduction of protamine zinc insulin (P Z I) Subsequent research has been directed toward the discovery of more suitable preparations new substances being tried to replace protamine Thus globin zinc insulin is a compound of insulin and globin

Table 9 Seven Insulin Preparations

Type of Insulin	Description	Indication	Action starts (hr after dose)	Effect lasts (hours)	Hypoglycaemic reactions
Soluble insulin	Pure crystalline insulin prepared from mammalian pancreas pH 2 5 3 5	All diabetic crises—especially severe ketosis and diabetic coma Many children and adults and insulin resistant cases	½ 1	6–8	3 hours after injection
Globin insulin	Soluble preparation of insulin with globin and a trace of zinc chloride Buffered at pH 3 0 3 2	Infrequently used by most workers	1	12 18	Late afternoon after morning injection
Protamine zinc insulin	Insoluble complex formed by insulin with protamine and the addition of a small quantity of zinc Buffered with phosphates at pH 6 9–7 3	Prior to use of I Z S frequently given as single injection if dose required not above 40 units Commonly used with soluble insulin as single mixed daily dose in approximate proportions of 2/3 sol to 1/3 P Z I	6–8	24 +	Late afternoon evening or during the night after morning injection

Isophan ul n (N P H)	Cry t ll p tam nsu In c mple w th n ex ess f protam De gnat d N P H N utr l m act on (N) C nt n g pr t m (P) M d hed t y H gedorn (H)	S ngl m ning nject on g es sat fact ry 24 hou cont ol n many ases Wid ly sed in U S A not e ten v ly ed n th s c u try	2	24 30	l te fternoon aftermorn ng in ject n
I Z S (am h) Sem l t)	S pe f am rphous part l of n n ul n z mpl in n a tate l uff r at 2 5	Oc a onally req ed wte t n lar l 3 m tu e not sat fact ry an l s met mes se n fa ty l se	1 2	12 16	3 4 hours aft r nject on
I Z S Lente	M tu e f am rph u an l ryst l e part cles of an in I n n o nplex n a t te l ff pr port n f 3 parts m rph t 7 p rts cry tall ne	M t aluat le long act ng n s l n p epa at n a a lal le S t ble for the m j rty f new case l at nts o oth r rég m m y be l nged to I Z S w th l secret on	1 2	24 +	M d morn ng r aft rnoon fter m rn g njec t on
I Z S (ry tall ne) I lt al nt	Su pen n f ry t ll ne In z n c mplex n an a et te l ff t pH 7 2 t 5	Oc a nally r q red wl en stan la d 3 7 m xt re t ati fa t y	4 0	30	12 18 h urs after nject on

with a trace of zinc chloride and Isophane (N P H) insulin is a crystalline protamine insulin complex but in contrast to P Z I it contains practically no excess of protamine It combines much of the immediate effect of soluble insulin with the prolonged effect of protamine zinc insulin so that a single injection of isophane insulin may persist for 24 hours

The new insulin zinc suspensions were the result of a discovery by Hallas Møller and his colleagues (1952) at the Novo Laboratories in Copenhagen that insulin in the presence of a very small quantity of zinc is less soluble at blood *p*H than protamine insulin provided anions such as phosphate and citrate are not present Using acetate buffer instead of the phosphate buffer previously used in P Z I Hallas Møller was able to prepare a suspension of pure insulin at blood pH in the presence of small quantities of zinc (1 mg per 1 000 units) but without protamine or globin Further work showed that the length of action of such preparations varied with the form of the insulin—amorphous insulin zinc suspension has a short duration of activity and crystalline insulin zinc suspension has a longer action The former preparation has been named insulin zinc suspension (semi lente) and the latter insulin zinc suspension (ultralente) Furthermore these preparations are miscible to produce preparations with intermediate ranges of activity and it has been found that the most useful proportion in which to mix the preparations is 3 parts of the amorphous I Z S to 7 parts of the crystalline I Z S such a preparation being known as insulin zinc suspension (lente) and frequently referred to as lente insulin

Choice of Insulin Preparation

Before the insulin zinc suspensions were available the most common method of insulin therapy in this country in recent years was a single mixed dose of soluble and protamine zinc insulin (in the approximate proportion of 2/3 soluble to 1/3 P Z I) Globin insulin has only been used in adults by a few workers though it has been more commonly used in children while in the U S A Isophane (N P H) insulin has been widely

used since its introduction. There have always been cases unsuitable for any form of long acting insulin treatment and requiring two or more daily injections of soluble insulin.

Considerable experience has now been gained in the use of the insulin zinc suspension and these preparations are probably the most satisfactory long acting insulins available.

1. The New Case Requiring Insulin. The majority of new cases presenting at diabetic clinics in this country and requiring insulin are now stabilized on one of the insulin zinc suspensions. In most cases Lente insulin (mixture of semilente and ultralente insulin in the proportion of 3 : 7) is satisfactory. It is occasionally necessary to use other proportions of semilente and ultralente or to use two single injections of the relatively short acting semilente preparation. A few cases will be found in whom satisfactory control is only obtained with two or more daily injections of soluble insulin.

Lente insulin can be started equally well in out-patients as in ward cases. There is much in favour of out-patient stabilization because the patient's insulin requirements can then be determined under his normal living conditions, but severe cases and those where the intelligence is low must be stabilized in hospital. The initial daily dose of Lente insulin is usually in the region of 12–16 units and the intelligent out-patient may be instructed to increase this by four units on alternate days according to his urine tests until he is seen in the clinic a week later. In hospital where facilities exist for blood sugar estimations and more frequent urine examinations the dose may be increased more boldly.

2. The Long-standing Insulin Case. When a long-standing diabetic comes under one's care by transfer from another clinic and is already well controlled it is usually injudicious to alter his treatment until there is some definite indication for doing so. It has been found, however, that the change to Lente insulin can be made without difficulty in most cases, although the total insulin dose may be greater on the new regime. On changing patients to Lente insulin from two doses of soluble insulin or from a mixed dose of soluble insulin and P.Z.I., an increase of about 10 per cent in total insulin dose is usually required and in patients previously on

a single dose of P Z I a much larger increase is often required

The introduction of Lente insulin should result in an increasing number of diabetics being adequately controlled on one insulin injection a day There are situations however where Lente insulin fails to control hyperglycaemia First there are cases already referred to which are relatively insensitive to the long acting insulin preparations and they cannot successfully be treated for any length of time without the use of soluble insulin Secondly it has been found that any form of severe diabetic ketosis is difficult to control with Lente insulin and in general patients requiring a total daily dose of more than 80 units of insulin should be treated with soluble rather than Lente insulin

Table 10

Duration in hours	*Insulin*
8	Soluble
10	N P H Semilente (Novo)
16	Globin Lente (Novo)
18	P Z I Ultralente (Novo)

Duration of action of insulins after Gerritz n F (1953) *Brit med J* 2 1030

Thus from the practical point of view although there are now seven insulin preparations on the market the requirements of most cases can be met by the judicious use of the insulin zinc suspensions while soluble insulin remains the preparation for the treatment of diabetic coma and severe degrees of ketosis—and for such other times of crises as operation periods and confinements and for those cases where long acting insulin preparations are not satisfactory

It should be emphasized that many factors influence the duration of action of the various insulins in different patients The larger the dose of any type of insulin the longer is the

effect likely to last (Lawrence 1955) Furthermore each patient s individual sensitivity to insulin is variable and the duration of action of any insulin preparation in practice is likely to differ from the duration found by Gerritzen (1953) in his experiments on non diabetic subjects (see Table 10) The determination of the correct insulin preparation and dose for each individual must therefore be achieved by the method of trial and error

Oral Hypoglycaemic Agents

The observation that certain sulphonamides may exert a hypoglycaemic effect was first made in 1942 by Janbon and his colleagues in Montpellier They were treating patients with typhoid fever with *p* aminobenzenesulphonamidoiso propylthiodiazole (I P T D) and a number developed severe hypoglycaemic symptoms Loubatières (1955) showed that in dogs the complete removal of the pancreas prevents the hypoglycaemic action of the drug although it was capable of augmenting the utilization of glucose in the partially depan creatized dog Sulphonamides were not used however in the treatment of diabetes until a chance clinical observation by Franke and Fuchs (1955) led them to try the effect of N_1 sulphanilyl N_2 *n* butylcarbamide (Nadisan B/55 Carbuta mide) in a series of diabetic patients They had been investi gating the antibacterial properties of certain new sulphona mides and found that this particular preparation tended to cause hypoglycaemic reactions They confirmed that it also controlled hyperglycaemia and glycosuria in certain diabetics and they found that the related substance N_1 *p* tolyl sulphonyl N_2 *n* butylcarbamide (D860 Orinase Tolbuta mide) had a similar effect although it is not a sulphonamide and has no marked antibacterial activity (see Table 11)

Mode of Action Loubatières (1955) suggested that I P T D might have a dual action on the islet cells of Langer hans—that of stimulating the secretion of insulin by the β-cell and depressing the secretion of glucagon by the α-cell B/55 may well act in the same way but Mirsky (1956) has shown that B755 and related substances are non competitive inhibitors of insulinase and that a diminution in insulinase

activity is associated with the hypoglycaemia induced by these substances

Young (1956) has pointed out that not only certain sulphonamides but also penicillin guanidine derivatives and acridines possess some degree of hypoglycaemic and antidiabetic action All these possess some antimicrobial action and he asks whether the two factors may be related Admittedly the antidiabetic action and the antibacterial effect

Table 11 ORAL HYPOGLYCAEMIC SULPHONAMIDES

$H_2N-C_6H_4-SO_2-NH-C(=N)-S-C-CH-(CH_3)_2$

I p aminobenzenesulphonamidoisopropylthiodiazole
(-I I T D 54RP P A S I T)

II $H_2N-C_6H_4-SO_2-NH-CO-NH-(CH_2)_3-CH_3$

N_1 sulphanilyl N_2 n butylcarbamide
(B/55 Nadisan Carbutamide)

III $CH_3-C_6H_4-SO_2-NH-CO-NH-(CH_2)_3-CH_3$

N_1 p tolylsulphonyl N_2 n butylcarbamide
(D860 Orinase Tolbutamide)

iveness of the sulphonamides are not quantitatively related and D860 has no obvious antibacterial action On the other hand he points out the possibility that the substance which is effective in the tissues might be a metabolite of that which has been administered rather than the administered drug itself At present however the exact mode of action of the antidiabetic sulphonamides is not known and the suggestion by Best that they may be hypoglycaemic partly because they facilitate the action of insulin and partly because of a hepatotoxic effect is disquieting

Clinical Application The clinical usefulness of these oral hypoglycaemic agents is strictly limited In Germany where

it is probable that too many diabetics have previously been treated with insulin. Bertram (1955) was able to claim the successful transfer of a large number of insulin controlled patients to oral hypoglycaemic agents. He admits, however, that most of these cases were obese middle aged diabetics, many of whom should have been adequately controlled on diet alone.

Workers in this country (Duncan, Baird and Dunlop, 1956; Wolff, Stewart, Crowley and Bloom, 1956; Hunt, Oakley and Lawrence, 1956; McKenzie, Marshall, Stowers and Hunter, 1956; Walker, Leese and Nabarro, 1956; Murray and Wang, 1956) have all confirmed that it is only in the mild relatively easily stabilized cases that the drugs are effective. Such patients are usually the patients whose insulin deficiency is relative rather than absolute. The oral hypoglycaemic agents at present available are thus no replacement for insulin. They must never be used in the treatment of the acute young diabetic who is absolutely deficient in insulin. Nor must they be used in patients with any degree of ketosis. In addition to these limitations on their usefulness the oral hypoglycaemic drugs have other more positive disadvantages. Agranulocytosis and thrombocytopenia have both been observed in patients treated with Carbutamide and its use has largely been abandoned in favour of tolbutamide which appears to be less cytotoxic. Unfortunately, it is also rather less efficient as a hypoglycaemic agent—but there is certainly a small group of mild diabetics whose hypoglycaemia and glycosuria is not quite adequately controlled by dietary measures who are improved by tolbutamide in a dose of 1·0–2·0 G daily.

It is probable that further oral hypoglycaemic agents will appear and at present chlorpropamide (Diabinase) is one with some promise of success. At present, however, these drugs should not be initially prescribed outside diabetic clinics.

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CHAPTER VI

DIABETIC KETOSIS

JOSLIN (1952) has pointed out that the term diabetic coma has been rather loosely used to indicate a severe degree of diabetic ketosis and he has arbitrarily defined a case as coma when the CO_2-combining-power is 20 vols per cent or lower (9 milliequivalents per litre). He chose this level because in the pre-insulin era he found that most such cases died whereas less severely acidotic cases recovered (Joslin 1918).

The treatment of a severe case of diabetic ketosis must still be regarded as one of the major medical emergencies. The management of each case is a matter for individual consideration and close supervision should be exercised by a physician experienced in the handling of such cases. It is not right to leave junior residents in charge (Graham 1950).

It is useful to consider at this point the circumstances in which a dangerous degree of diabetic ketosis may develop.

(1) A new case of diabetes mellitus may present in diabetic coma or pre-coma.

(2) A known diabetic may become ketosed for a variety of reasons.

(*a*) A diabetic who persistently ignores the rules of diet and insulin dosage laid down by his medical advisers may well develop ketosis.

This occurs most commonly amongst patients of low intelligence and amongst those who may have a resentment against their disease to the point of wilful non-cooperation.

(*b*) An intercurrent infection may precipitate diabetic coma or pre-coma in a previously well stabilized patient. The types of infection most liable to cause this are pneumonia, acute gastro-enteritis and extensive staphylococcal infections such as *carbuncles or ischio-rectal abscesses*.

(c) A previously well stabilized patient may sometimes pass into a phase of insulin resistance and develop ketosis if his insulin dose is not increased accordingly

Reviewing the precipitating cause of severe diabetic ketosis in a series of 67 cases to the Massachusetts General Hospital Harwood (1951) found that the most frequent cause was infection Long continued neglect of the diabetic regimen was nearly as common and one third of the patients had neglected to take their insulin for a period of one to three days prior to admission One half of the patients developed ketosis as a result of the combination of more than one factor There were 13 patients whose diabetes had not previously been diagnosed

It should be pointed out that it is the severe insulin deficient diabetics who are most liable to develop serious degrees of ketosis The so called brittle diabetic who is liable to wide variations in blood sugar and usually a severe case taking large amounts of insulin is always a candidate for either severe hypoglycaemic reactions or for severe diabetic ketosis

Diagnosis of Diabetic Ketosis

There should be little difficulty in making a diagnosis of diabetic ketosis—but the following symptoms and signs are characteristic

1 **Onset** Except in rare cases the development of serious ketosis takes place over a period of 24-36 hours so that on this account alone it should never be confused with hypoglycaemia During this period the patient may complain of nausea anorexia vomiting excessive thirst and polyuria or abdominal pain The last is responsible for the rare syndrome the actue abdomen of the diabetic

2 **Dehydration** In the early stages of ketosis there is a greatly increased urinary output though by the time the patient is admitted to hospital there may be a state of oliguria and signs of dehydration may be marked The lowered eye ball tension has long been regarded as pathognomonic of diabetic dehydration but the parched and shrunken tongue

is even more characteristic The extreme dehydration of the severe case give the patient an appearance suggestive of a malignant cachectic state

3 The Circulation Chiefly as a result of the dehydration the pulse rate is rapid and low in tension and the blood pressure is low and sometimes unrecordable The skin feels cold

4 Respiration In severe ketosis there is a marked increase in the respiration rate often described as air hunger (Kussmaul s respiration) This is a further factor in increasing the dehydration and sometimes an odour of acetone can easily be detected in the breath and the older physicians are credited with walking into the ward sniffing the air and asking to see the case of diabetic coma

5 Level of Consciousness Most cases of diabetic ketosis are rousable on admission to hospital and the patient deeply unconscious in diabetic coma has a poor prognosis

6 Urine Examination The examination of the urine for sugar and ketone bodies should confirm the diagnosis The urine will be loaded with sugar and Rothera s test the acetest tablet test and Gerhardt s test will be positive for ketone bodies The urinary chloride content will be found to be low and probably less than 2 G per litre

7 Blood Sugar Estimation If it is not possible to obtain a specimen of urine because of oliguria a blood sugar estimation is vital and blood sugar control of the treatment is by far the most satisfactory for the first 24 hours The initial blood sugar level is likely to be 400 mg per 100 ml or greater

PRINCIPLES OF TREATMENT

Apart from treating any obvious infective precipitating cause of the ketosis the most urgent measures are the correction of the dehydration and the administration of large amounts of insulin

Before considering the detailed management of a case the principles involved in the correction of the dehydration the best methods of administering insulin and the place of carbohydrates in the treatment of diabetic ketosis will each be discussed

1 Correction of Dehydration and Electrolyte Balance In

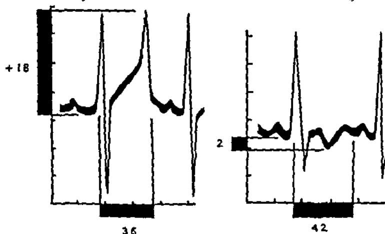
the past the correction of dehydration in severely ketotic diabetic patients has frequently been carried out with normal saline and in general the results have been satisfactory A few cases have however collapsed and died after showing an initial satisfactory response Investigation has revealed that a more profound electrolyte disturbance is associated with diabetic ketosis than had previously been recognized In particular the role of potassium is of the greatest importance and it is believed that many patients dying in the second 12 hours of treatment do so because of a lowered serum potassium level (Holler 1946) These patients have frequently shown the characteristic clinical feature of hypokalaemia —namely extreme weakness followed by sudden death due to paralysis of the respiratory muscles In the phase of severe dehydration it has been shown that potassium leaves the cells and potassium is lost in the urine. Because of this migration of potassium from the cells there may be an initial rise in serum potassium but when dehydration is corrected the cellular affinity for potassium is restored and hypokalaemia may develop

In considering the most efficient way of correcting the dehydration in diabetic coma it is therefore wise to consider first the restoration of extracellular fluids and electrolytes and secondly the restoration of cellular depletion (Nabarro Spencer and Stowers 1952) In this respect it is important to bear in mind the fact that renal function is depressed during this phase of acute circulatory collapse which accompanies extracellular fluid depletion and that during this phase there is a protective inhibition of potassium excretion At this state therefore it is dangerous to give large amounts of potassium because of the potential danger of potassium poisoning Cardiographic changes are shown in Fig VI 1

Replacement of Extracellular Fluid Although isotonic saline solution is the fluid that has previously been used most commonly for the rapid replacement of the extracellular fluid loss that is directly responsible for the severe circulatory collapse it is theoretically not the best solution Nabarro *et al* (1952) have suggested that it is better to use a saline lactate solution containing sodium chloride 5 85 G and sodium

lactat 3 of C with distilled water to 1 litre The lact te l elps to correct the severe degree of acidosis which is present an l in tl e proportion a lvised does not cause alkalosis

Cell lar Restoration As already pointed out there is a m gration of potassium from the cells to tl e plasma durin the d velopment of severe d abetic ketosis A similar migra



fr ad et al

HYPERKALAEM A
T wa e n rea ed amp tu l
w n w t ase QT t al
n n l

H P KALAEM A
T wa e n e t l QT n er al
t g l

l G 11 H pe ka m usua p esent at the beg n ng f t m nt f d t ma l t h j ka m a de k p l t th p m n l a an l p ta m e ted n t urin

t n f mag es m an l ph sph tes al o takes plac O ing to th extrarenal uraemia wh ch acc mpan s the severe deh dration th urinary exer tion f th se electrolyt s may be d pr ss l an l th h gh pla ma l vels which may init ally be present g v a par l xically false impres n of the ab-s l ite l fici ncy wh ch act ally exists It i nly after the rest rat n of th extrac ll lar flu l t at normal renal func ti n is rest r l an l excr ti n of th se i s l a l t l plasma l vels It i at th s p nt that it i important to in titute m asures t r t r the c ll lar lectr lytes especially

potassium At this stage a cellular repair fluid should be given Nabarro *et al* (1952) have suggested that such a solution should contain potassium phosphate and magnesium with sodium and chloride to cover continuing urinary loss of these electrolytes They suggest the following solution

Sodium chloride	1 17 G
Dipotassium hydrogen phosphate	0 87 G
Potassium chloride	1 49 G
Magnesium chloride	0 24 G
Glucose 50 G	
Distilled water to 1 litre	

Provided an adequate urine output has been re established it is advisable to begin administration of this solution when the blood sugar begins to fall at a rate of 1 litre every 4-6 hours When the patient is able to take fluids by mouth potassium supplement may be provided in a mixture containing 50 G glucose and 2 G of dibasic potassium phosphate in 500 ml of water flavoured with orange juice Up to 2 litres of this mixture may be given daily

2 *Insulin Administration* Although the most striking feature of the severely ketotic diabetic patient is the extreme degree of dehydration and circulatory collapse it must not be forgotten that the primary defect which has permitted the development of this state of affairs is an inadequate amount of effective insulin Close therefore upon the urgency of correcting dehydration comes the urgency of administering insulin in adequate amounts

Root (1945) has shown that the speed with which large amounts of insulin are administered may affect the outcome of the case Thus the mortality rate in a group of cases receiving an average of 216 units in the first three hours of treatment was 1 6 per cent as against 12 per cent in a comparative series receiving an average of only 83 units in the same time

It is useless to rely on subcutaneous insulin injections in the early state of collapse Some authorities advise giving all insulin intravenously in the early stages (Black and Malins 1949) but as it is believed that intravenous insulin is

rapidly destroyed it is necessary to give injections as often as once hourly if all the insulin is administered by this route Most workers prefer to give part of the insulin by the intravenous route and part by intramuscular or deep subcutaneous injection Certainly a proportion of the first dose should be given intravenously

The total initial dose in a severe case should never be less than 100 units and it must be stressed that no preparations other than soluble insulin is suitable for treating diabetic ketosis Insulin treatment should be started as soon as a clinical diagnosis of diabetic ketosis has been reached and the administration of the initial dose of insulin should not be deferred until the result of a confirmatory blood sugar estimation is available An immediate blood sugar estimation must however be carried out and subsequent doses should be decided upon in the light of the blood sugar levels If the first reading is alarmingly high say 800 mg per cent or more it is quite safe and probably advisable to give a further 100 units (again part intravenously and part intramuscularly or by deep subcutaneous injection) forthwith If in two hours there has been no blood sugar fall the initial dose should be repeated if the level is higher it should be increased and if there has been a fall the dose should be proportionately reduced Assuming that the intramuscular or deep subcutaneous routes are being used the interval between later doses of insulin should be between two and four hours and except in cases of great severity the four hourly interval is both convenient and safe and allows time for biochemical estimations to be carried out so that the results are available just before the next dose falls due

3 The Place of Carbohydrates Although the blood sugar is high and the tissues presumably saturated with sugar there are those who advise the use of glucose in the intravenous infusions from the beginning of treatment (Soskin and Levine 1946 Danowski *et al* 1946) These workers believe that carbohydrate metabolism is accelerated by what Himsworth (1940) has described as the head of carbohydrate pressure On the other hand hyperglycaemia produces cellular dehydration and a continuing osmotic diuresis with excessive

loss of water, glucose and sodium chloride in the urine This uncontrolled renal drain of water and electrolytes delays the restoration of body fluids in spite of intensive parenteral therapy (Nabarro *et al* 1952 Seldin and Tarail 1950)

It is therefore more generally accepted that glucose should be withheld until the blood sugar has fallen to some arbitrary figure such as 300 mg per 100 ml after which it should be given generously Among the advocates of this view are Joslin (1952) Graham (1950) and Butler (1950)

In recent years several American workers have advocated the use of fructose instead of glucose in the early stages of treatment Nabarro *et al* (1955) review the literature and report the results of giving insulin and intravenous fructose to five patients with severe diabetic ketosis and compared the results with 5 patients treated without fructose They conclude that at present there is no reason for including the early administration of fructose in the routine treatment of severe diabetic ketosis

Detailed Management of the Case

Although it has been stressed that the treatment of each case of severe diabetic ketosis is a matter for individual consideration and the more important general principles have been discussed it is well to have a general plan which may be applied to any case

A Immediate Treatment

On making a diagnosis of severe diabetic ketosis on the history physical examination and urine tests the following measures should be instituted forthwith

1 **Insulin Administration** 100 units of soluble insulin should be administered—40 units intravenously and 60 units intramuscularly

2 **Intravenous Therapy** This should be established immediately and except in old persons the first litre of sodium lactate solution should be run in as fast as it will run and if possible in less than half an hour The second litre should be run in nearly as rapidly If there is difficulty in finding a vein the subcutaneous route with the help of Hyalase may be used

FIG VI 2 DIABETIC COMA CHART NAME

Dat	R	P Cl	T E T co2	Cl	pH	OD Electrolytes on at		ins ven	N EE	UT
a.m										I
a.m.									ml	
oo									I	I sens oss
3 p m										
6									T tal	T tal ml
m										
n.									C I	
3 m										
te										1 In ml
6 m										
9 m									al ml	V mit
oo									I	Insens loss
3 m.										
m									I ml	T tal
p m.										
M n.									H G	
m.										
D										T ri ml
6 m.										sp
8 m									ml	V mit
oo										I se os
3 m										
p m.										
6 m.									ta ml	T tal ml.
M dn.									CHO G	
3 m.										

until an intravenous route has been established if necessary by the cut down technique

3 *Stomach Washout* If there is vomiting stomach wash outs should be carried out with 5 per cent sodium bicarbonate solution and a Ryle s tube passed and aspirated ½ hourly

4 Antibiotic Therapy Even though the precipitating cause of ketosis may not have been infective there is grave danger of infection supervening For this reason 1 000 000 units of crystalline penicillin should be given on admission and 500 000 units thereafter twice daily

5 Laboratory Co operation The laboratory must be informed that a case of diabetic ketosis has been admitted and their full co operation requested

Simultaneously with the administration of the first intravenous dose of insulin blood should be withdrawn so that the following estimations may be carried out

(1) Blood sugar
(2) Blood urea
(3) Electrolyte values—serum sodium potassium and chloride
(4) CO_2 combining power
(5) Haemoglobin level
(6) White blood count and differential
(There is always a moderate leucocytosis with a polymorphonuclear leucocytosis)
(7) Blood grouping

6 Urine Examination There may be extreme difficulty in obtaining urine specimens in the early stages of treatment owing to the oliguria but every effort should be made to obtain a specimen The volume of all specimens must be measured and recorded and all specimens must be tested for sugar, ketone bodies (both by Rothera and Ferric chloride tests) and chlorides It is convenient to record the laboratory findings treatment given etc on a chart as illustrated (Fig VI 2)

B Subsequent Management

As already indicated there is lack of agreement on the time interval between subsequent doses of insulin but the following

scheme adapted from the plan suggested by Nabarro *et al* (1952) is one which can be modified to suit the requirements of any case under treatment (See Table 1) In particular the interval between blood sugar samples could be well increased in less serious cases

Table 1

Time	*Blood Sugar*	*Insulin*	*i v Infusion*
0 hours	Sample taken	100 units	Saline lactate 1 lit in 1st ½ hour 1 lit in next ¾ hour
½ hour	Result If 400 mg per cent +	100 units	Continue saline lactate
1 hour	Sample taken	—	Continue saline lactate
1½ hours	Result		
	If going up	00 units	Continue saline lactate
	if same	100 units	Continue saline lactate
	if going down	nil	Start glucose containing fluid
hours	Sample taken	—	—
2½ hours	Result		
	if going up	400 units	Continue saline lactate
	if same	100 units	Continue saline lactate
	if going down	nil	Start glucose containing fluid
Continue hourly if blood sugar results are			
	going up	twice last dose	Saline lactate
	same	100 units	Saline lactate
	going down	nil	Glucose fluid

Rate of Administration of Fluids

1 *Saline lactate*

1st litre	½ hour
nd litre	1 hour
3rd litre	2 hours
subsequent litres	4–6 hours

Glucose Cellula Repair Fluid

Rate 4 6 hours per litre

This fluid must only be used when the blood sugar has fallen to 300 mg per 100 ml and when the renal flow is adequate (more than 50 ml per hour)

If the renal flow is inadequate but the blood sugar is falling the saline lactate solution may be continued with the addition of glucose in the proportion of 50 G to the litre

When the blood sugar has reached relatively normal figures and the circulation has been restored to normal and a satisfactory urine output re established it is safe to start feeding by mouth. At first this should be with fluids only but fairly quickly a normal diet should be resumed with a generous carbohydrate content (180–200 G). This should at first be given equally spaced throughout the hours when the patient is awake and it is convenient to divide the 24 hours into four six hourly periods with insulin being given as necessary three to four times. Once the renal threshold has been found to be approximately normal the test for sugar on urine specimens collected over the half hourly period before the insulin is due are reliable indications of the dose required. It is convenient to decide upon a basic dose to be given at 6 a m and 6 p m with supplementary doses at mid-day and midnight if there is glycosuria at these times. Within a few days of reaching this stage it is usually possible to re stabilize the patient on a diet and insulin dose (probably with long acting insulin) on which he will be able to leave hospital.

It is important to appreciate that a patient in diabetic coma has suffered from profound circulatory failure and that complete bed rest is essential for a minimum period of one week after recovery (Cooke 1948).

(The plan by which the day is divided into four six hourly periods and by which insulin is administered six hourly is convenient for the treatment of the less serious cases of ketosis and for covering other crises in a diabetic patient's life such as surgical operations labour and the puerperium or severe inter current infections.)

Unexpected Hazards in the Treatment of Diabetic Ketosis

Shock The patient in untreated diabetic ketosis may become severely shocked and pass into a phase of extreme circulatory collapse. The blood pressure falls the pulse rate increases and the patient becomes cyanotic. Such a state of collapse may occur at any time in the early phases of treatment even when therapy seems to be progressing well and before any fall in the serum potassium has yet taken place.

In these cases transfusions of whole blood or plasma should be used to sustain the blood volume and may sometimes prove life saving More recently the nor adrenaline drip (4 mg per litre) has proved of value in such cases

Gastric Dilatation Patients with severe diabetic ketosis are liable to develop acute gastric dilatation and haemorrhagic gastritis This may occasionally result in disastrous circulatory collapse and in such cases it is urgent to perform gastric lavage The dramatic restoration of the circulation within a few minutes of this procedure is a most satisfactory experience for the physician though the exact mechanism whereby it is brought about is not clearly understood

Pulmonary Oedema Throughout the discussion of the treatment of diabetic ketosis great stress has been placed on the importance of rapidly correcting dehydration It is only rarely that any adverse effects result from rapid intravenous infusions Nevertheless in the presence of myocardial damage it is possible to precipitate acute pulmonary oedema and a dangerous rise in venous pressure by too rapid infusions This is particularly liable to occur in the elderly and in these persons or in patients previously known to have cardiac disease it is essential to modify the rate at which dehydration is corrected by the intravenous route Unfortunately the subcutaneous route is of limited value in correcting the state of circulatory collapse which exists and the prognosis in the elderly patient with severe diabetic ketosis is very poor indeed It is essential in these cases to observe the jugular venous pressure and to keep a close watch for the appearance of dependent rales or sacral oedema

Hypoglycaemia The swing from hyperglycaemia to hypoglycaemia is liable to occur when the circulation has been restored towards normal and when large doses of insulin which have been given intramuscularly or deeply subcutaneously become suddenly available It is always undesirable to have a sudden lowering of the blood sugar to hypoglycaemic levels because such a lowering tends to be followed by compensatory hyperglycaemia due to the release of adrenaline Furthermore the cortical cells may have become accustomed to a high blood sugar level and hypo

glycaemic symptoms may occur at blood sugar levels higher than those normally regarded as hypoglycaemic. It is in children that sudden hypoglycaemia may be particularly dangerous and much smaller doses of insulin should be used in the case of ketotic children than in adults. Children are usually extremely insulin sensitive and the dose required is often much smaller than the proportion of the adult dose that might be calculated from their smaller weight. In my own experience a child aged 8 years admitted in severe ketosis with an initial blood sugar of 700 mg. per 100 ml. became unconscious after the administration of a total of 50 units of insulin (20 units being given on admission, 20 units four hours later and 10 units four hours after this). A blood sugar taken just after he became comatose was 60 mg. per 100 ml. and although he was given intravenous glucose and his blood sugar raised to 250 mg. per 100 ml. within half an hour he remained uncoscious for twelve hours.

The Treatment of Diabetic Ketosis in the Home

Although any severe case of diabetic ketosis must be admitted to hospital it is often possible for the practitioner to prevent such a state of affairs developing by being aware of the precipitating causes and being able to institute treatment which will correct the condition at any early stage. A diabetic who develops an infection should be instructed to test his urine before each meal. In cases of mild infection it may be possible to continue to control any increased glycosuria by raising the patient's ordinary morning dose of insulin—or in the case of patients on two doses of soluble insulin—by an increase in each of these doses. In these circumstances it is usually safe to start by increasing the total daily dose by 10–20 per cent.

If, however, the infection is severe and especially in the presence of diarrhoea or vomiting, the patient should be immediately transferred to soluble insulin given if necessary at six hourly intervals and if the patient is unable to take solid food, a fluid diet containing 180–200 G. of carbohydrate daily should be prescribed. In the presence of ketosis it is desirable to give added salt and the diet may then be pre

pared by making up the carbohydrate in half strength normal saline flavoured with fruit juice. Such a preparation may be roughly prepared in the home by adding one half teaspoonful (.7 G.) of salt to one pint of water (570 ml.). The carbohydrate must be spaced at regular intervals throughout the day and it is often convenient to aim at giving 10–15 G. hourly. Some suggestions for a fluid diet are given in Table 7 Ch. X on p. 62. Initially the six hourly insulin dose should be one third of the normal daily dose and must be adjusted at each dose according to urine tests which must be carried out both for sugar and for ketones before each insulin dose is due. In order to determine the correct insulin dose it is essential to observe what may be described as the 'half hourly collection rule'. Thus the bladder should be emptied half an hour before the insulin dose is due, this specimen being rejected and another collected immediately before the injection and tested for sugar. It is upon the result of this test that the dose of insulin to be given must be decided.

e.g.

If the specimen contains	1–2 per cent	Increase previous dose by 10 per cent.
If the specimen contains	0.5–1 per cent	Give same insulin dose.
If there is less than	0.5 per cent	Reduce or omit insulin at doctor's discretion.

It is particularly important to stress that insulin must never be withheld from a diabetic who is vomiting and unable to take food. These patients are those most likely to become ketosed and to pass into diabetic pre-coma or coma. In the case of any diabetic who is unable to tolerate even a fluid carbohydrate diet it is vital that hospital admission should be urgently arranged so that intravenous therapy may be instituted. So long as the practitioner is certain of the diagnosis in these cases it is safe and may even be life saving

to give the pre comatose diabetic patient a large dose of insulin while awaiting the ambulance—the dosage being something in the order of 50 units intravenously and 50 units by intramuscular or deep subcutaenous injection Although there should never be any possibility of confusing diabetic coma with hypoglycaemia it is only right at this point to repeat the warning that if any unconscious hypoglycaemic patient is given a large dose of insulin it may be sufficient to cause profound cerebral hypoglycaemia with irreversible changes and death

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CHAPTER VII

HYPOGLYCAEMIA

HYPOGLYCAEMIC reactions constitute one of the greatest inconveniences to diabetic patients taking insulin and are also a source of anxiety to their medical advisers, their families and their employers. They may render the individuals unsuitable for certain types of employment and in particular they may make them unsuitable as drivers of vehicles. It is therefore of the utmost importance for the patient and his doctor to be aware of the symptoms and signs of hypoglycaemia and to be familiar with the likely precipitating causes and able to treat attacks.

Most persons experience symptoms of hypoglycaemia when the blood sugar level is below 60 mg. per 100 ml. Occasionally the sudden lowering of the blood sugar from a high level may cause hypoglycaemic symptoms to occur at a higher level, but this is probably rare. On the other hand, some diabetic patients seem able to tolerate low blood sugar levels and it is not uncommon to find figures of 60 mg. per 100 ml. or lower on routine blood sugar estimations in the diabetic clinic and to find that the patients deny any symptoms whatever. The most characteristic symptoms are produced by a sudden fall in blood sugar level, so that these are most frequent when soluble insulin is being used, the longer acting insulins tending to give slightly modified symptoms.

In the following sections the symptoms of hypoglycaemia are described. In spite of their variety it is fortunately true that a hypoglycaemic reaction tends to run a fairly constant pattern for each individual. He thus learns to recognize the symptoms of danger, and in most cases can take carbohydrates in some easily assimilated form and prevent the development of hypoglycaemic coma. There are, however, some unfortunate patients who are so sensitive to insulin that when hypoglycaemia develops they pass rapidly into coma.

is always in an advanced state of dehydration. The presence of sugar in the urine does not necessarily exclude a diagnosis of hypoglycaemia, as the bladder may not have been emptied for several hours, but any doubt will be dispelled by a blood sugar estimation.

7. After effects. Deaths from hypoglycaemia should be extremely rare and usually occur when the condition is misdiagnosed as diabetic coma and treated by further insulin administration, as occurred in the case described by Winkler (1948). Profound prolonged hypoglycaemia may, however, be followed by a period of aphasia and amnesia. Furthermore, the elevation of the blood sugar to normoglycaemic or even hyperglycaemic levels may not always be followed by an immediate return to consciousness. *In this respect it is worth recording the* case of a child of 8 who was admitted to hospital in diabetic pre-coma as the first manifestation of diabetes. The blood sugar was 700 mg. per 100 ml. 20 units of insulin were administered at 10 p.m., 20 units at 2 a.m. and 10 units at 6 a.m. At 8 a.m. the child had a fit and became comatose. The blood sugar was found to be 60 mg. per 100 ml. and intravenous glucose (50 per cent) was given immediately. The blood sugar level was quickly raised to 250 mg. per 100 ml. but in spite of this level being maintained he remained unconscious for 12 hours. In this case it was presumably the sudden lowering of blood sugar level which was responsible for the profound coma.

Precipitating Causes of Hypoglycaemia

The following are the common causes of hypoglycaemia due to insulin.

1. Administration of Incorrect Dose. The intelligent diabetic *who regularly gives his own insulin should rarely* make a mistake with his insulin dose. Occasionally, however, an overdose may result from confusion over the strength of the insulin or by inaccurate measurement, especially in the case of a patient with poor vision. Such patients usually devise some method of

marking the point on the syringe to which they should draw up the insulin A mark with a grease pencil or with a narrow piece of strapping are both useful methods

2 **Lack of Food** Patients taking insulin—and especially those taking long acting insulins must take food at regular intervals A patient who misses a meal especially if this occurs about the time of maximum activity of the insulin administered is liable to have a hypoglycaemic reaction Any patient who is likely to miss a meal should carry a reserve supply of carbohydrate—indeed all diabetics taking insulin should have an emergency supply of sugar—and patients who find it habitually difficult to get their evening meal at a regular hour are much safer on two doses of soluble insulin than on on any form of long acting insulin

3 **Unusual Exercise** Muscular exercise in any form results in a fall in blood sugar level owing to the increased calorie requirement and the diabetic who indulges in any form of sporting activity has to beware of hypoglycaemia and take measures to prevent it Such patients should either reduce their insulin dose or increase their carbohydrate intake before the intended exercise Many patients regularly reduce their insulin dose at the weekend to cover this contingency while others prefer to treat themselves to a large mid day meal in preparation for the afternoon s golf gardening or tennis In the case of school children particular care is required in giving advice so that they are not debarred from taking part in normal school activities

4 **Improved Carbohydrate Tolerance** The foregoing causes of insulin hypoglycaemia are easily understood and should be preventable There are however circumstances in which the carbohydrate tolerance improves and the insulin requirement falls, and in these cases it is more difficult for the patient himself to avoid hypoglycaemia although the intelligent patients can do a great deal by careful urine tests and by adjusting their insulin dosage

The circumstances in which an improvement in carbohydrate tolerance may occur are as follows

(a) *After Initial Stabilisation* It is a common experience for a new case of diabetes to be admitted to hospital for stabilization and to be found to require a considerable dose of insulin to control the glycosuria and hyperglycaemia On discharge from hospital such patients frequently find that on the same dose of insulin their urine tests are persistently sugar free and they may experience severe hypoglycaemic reactions if the dose is not reduced This may partly be explained by their increased activity on leaving hospital but this is certainly not always the full explanation because the insulin requirement is often found to fall progressively to a small proportion of that on which they were initially stabilized It must be assumed that these patients have partially regained their carbohydrate tolerance as a result of dietary restriction and insulin therapy Because of this aspect of the stabilisation of new cases there are those who advocate the out patient treatment of all new cases so that they may become stabilized under their normal living conditions

(b) *After a Period of Insulin Resistance* The phenomenon of insulin resistance is not fully understood but occasionally a patient s insulin requirement may rise to quite staggering figures (e g several hundred units a day) In those cases in which the largest doses are required there is usually no obvious cause for the resistance to insulin—but in a number of other conditions such as infections or periods of psychological stress there is a definite rise in insulin requirement which is probably due to the development of partial insulin resistance In these cases there is often a fairly sudden fall in insulin requirement and if this is not appreciated there is a danger of hypoglycaemia if the insulin dose is not appropriately reduced

(c) *After Pregnancy* During pregnancy there is usually a lowering of the renal threshold so that the glycosuria may be increased without any deterioration in the diabetic control but in the third trimester there is frequently a marked increase in insulin requirement Following delivery there is a

sudden fall in insulin requirement with consequent danger of hypoglycaemia

DIFFERENTIAL DIAGNOSIS OF HYPOGLYCAEMIA

1 **Diabetic Coma** There are few conditions which cause more anxiety to students and practitioners than the unconscious diabetic patient From what has already been said there should be little difficulty in differentiating diabetic from hypoglycaemic coma but at this point it would be well to summarize the outstanding clinical features of these two conditions (See Table I)

2 **Alcoholic Intoxication** As already pointed out the patient suffering from hypoglycaemia may behave as though drunk and it is important to differentiate the two conditions

3 **Gastro intestinal Haemorrhage** It must be rare for hypoglycaemia to be mistaken for gastro-intestinal haemorrhage but confusion can sometimes occur as happened in the following case A middle aged woman had been waiting several hours in a diabetic clinic and was finally seen by the doctor at about 11 30 a m She complained of tremor faintness sweating and palpitations Not unnaturally it was assumed that she was hypoglycaemic as she had missed her mid morning snack and had taken her usual morning dose of soluble insulin She was given a cup of milk and a biscuit and re assured The same afternoon she was admitted to hospital having vomited a bucket full of blood Emergency partial gastrectomy had to be performed and she was found to have a chronic duodenal ulcer

4 **Other Causes of Sudden Coma** Hypoglycaemic coma has to be differentiated from such other suddenly developing comatose conditions as subarachnoid haemorrhage cerebral haemorrhage or epilepsy followed by coma In most cases the differentiation is not difficult but blood sugar estimations may be required

Variation of Hypoglycaemic Symptoms with Type of Insulin

As already stated the most characteristic symptoms of hypoglycaemia occur after an injection of soluble insulin and the longer acting insulins often cause a more gradual onset of symptoms which at the same time may be more difficult to relieve and may require the repeated administration of carbohydrate before full relief is obtained

In considering the type of reaction that may be expected from the various insulin preparations it is necessary to consider their duration of effect and the time of their maximum activity

At the present time there are available in this country no less than seven different preparations of insulin Their duration of activity and times of maximum activity have been tabulated in Table 9 Chapter V From a clinical aspect however the times at which reactions most frequently occur do not always coincide with the times at which insulin activity has been found to be maximal by the experimental method

Soluble Insulin Reactions occur suddenly and usually 3-4 hours after an insulin injection Thus it is common for reactions following a morning dose to occur before lunch and following an evening dose to occur at bedtime

Protamine Zinc Insulin Reactions occur late in the day during the night or even before breakfast on the following morning In spite of the observation by Gerritzen (1952) that he has detected no insulin effect from P Z I after 18 hours it is a clinical fact beyond dispute that patients taking large doses of P Z I or a mixed dose of soluble and protamine zinc insulins may have early morning reactions Furthermore they can be severe and if the patient does not recognize that he is hypoglycaemic and gives his normal dose of insulin he may become unconscious before being able to take his breakfast

Globin Insulin This preparation has been shown by Gerritzen to be active for 16 hours and to reach its maximum activity at 3 hours The commonest time for clinical hypo-

glycaemia to be encountered is thus during the morning, but it is also common in the afternoon The times of 126 reactions from globin insulin taken before breakfast were analysed by Wauchope (1948) as follows

Midnight to 7 a m	12
10 30 a m to 1 p m	75
3 p m to 6 p m	30
7 p m to 10 p m	9

N.P H (Isophane) This insulin preparation has been little used in Great Britain though it has been the most frequently used preparation in the United States in recent years White (1949) stated that the hypoglycaemic hazard was chiefly nocturnal but late afternoon and evening reactions commonly occur

Insulin Zinc Suspensions Gerritzen (1953) has found that the duration of activity of Semilente insulin is 10 hours Lente insulin 16 hours and Ultralente insulin 18 hours Lente insulin (mixture of Semilente and Ultralente insulin in proportion of 3 7) is the most frequently used preparation and hypoglycaemic reaction may follow its use In a large series of cases from King s College Hospital Gurling *et al* (1955) report the times of 211 reactions after a morning dose of Lente insulin as follows

Breakfast to lunch	112
Lunch to evening meal	62
Night to breakfast	37
	211

Treatment of Hypoglycaemia

Most patients are able to recognize the early symptoms of hypoglycaemia and can relieve them by using their emergency lump of sugar (1 lump=5 G carbohydrate) or by bringing forward their next meal time As already stated the patient is sometimes able to recognize the symptoms but unable to take the necessary preventive measures Such patients should be given a cup of milk with sugar or biscuits If the patient has reached a state when he cannot easily be

fed by mouth the most satisfactory treatment is the intravenous injection of glucose in 50 per cent solution The injection should be continued until the patient has fully regained consciousness though in some cases especially if the patient has been unconscious for some time before receiving medical attention the coma may persist even though the blood sugar is restored to normal levels. This is particularly liable to occur when the hypoglycaemia is due to protamine zinc insulin

After the patient has regained consciousness an attempt must be made to determine the cause of the reaction

Table 1

	Diabetic Ketosis	*Hypoglycaemic Coma*
ONSET	Gradual usually over a period of 24 hours or more	Sudden especially with soluble insulin
DEHYDRATION	Marked with dry skin parched tongue and lowered eye ball tension	No signs of dehydration Moist skin often sweating Tongue moist Eye ball tension normal
CARDIOVASCULAR COLLAPSE	Usually marked with rapid thready pulse and lowered blood pressure	Usually a full bounding pulse and normal blood pressure
RESPIRATION	Characteristic Kussmaul breathing (air hunger) with smell of acetone in breath	Often quiet respirations but may be stertorous if coma is deep
REFLEXES	Often absent with flexor plantar responses	Usually brisk with extensor plantar responses Muscular twitchings and epileptiform seizure common
URINE	Heavy glycosuria acetonuria and often albuminuria Low urinary chloride level	Sugar free—certainly on ½ hourly collection after coming under observation Usually no acetone and normal urinary chloride level
BLOOD SUGAR	Raised 300–400 mg per 100 ml or more	Lowered 60 mg per 100 ml or lower
DEPTH OF COMA	Except in advanced cases patient usually rousable	Coma often deep

Spontaneous Hypoglycaemia

Any consideration of hypoglycaemia would be incomplete without including a brief reference to causes of hypoglycaemia other than those due directly to the administration of exogenous insulin. Thus there are many causes of endogenous hypoglycaemia and the more important are summarized in Table 2 and the subject has been fully reviewed by Conn and Seltzer (1955)

Table 2

I *Organic Hyperinsulinism*
- (1) Pancreatic islet cell adenoma
- (2) Pancreatic islet cell carcinoma
- (3) Generalized hyperplasia and hypertrophy of the islet cells of Langerhans

II *Functional Hypoglycaemia* ( )

III *Alimentary Hypoglycaemia*
- (1) After gastroenterostomy
- (2) After partial or total gastrectomy

} Due to rapid intestinal absorption

IV *Hepatic Disease*
- E g severe hepatitis cirrhosis

V *Anterior Pituitary Hypofunction* due to any cause e g hypophysectomy Simmond s disease etc

VI *Adrenocortical Hypofunction* due to any cause e g adrenalectomy Addison s disease sudden withdrawal of Cortisone therapy

VII *Renal Glycosuria*

VIII *Idiopathic Spontaneous Hypoglycaemia of Infancy*

From this table it is clear that hypoglycaemia may often be a manifestation of serious metabolic or endocrine disease. In these cases the primary condition is likely to manifest itself by other symptoms and signs and diagnosis should present no problem. In the case however of organic hyperinsulinism due to adenomatous carcinomatous or other hyperplastic changes in the islet cells and in the case of functional hyperinsulinism the presenting symptoms are usually due to hypoglycaemia and it is important and may be diffi

fed by mouth the most satisfactory treatment is the intravenous injection of glucose in 50 per cent solution. The injection should be continued until the patient has fully regained consciousness though in some cases especially if the patient has been unconscious for some time before receiving medical attention the coma may persist even though the blood sugar is restored to normal levels. This is particularly liable to occur when the hypoglycaemia is due to protamine zinc insulin

After the patient has regained consciousness an attempt must be made to determine the cause of the reaction

Table 1

	Diabetic Ketosis	*Hypoglycaemic Coma*
ONSET	Gradual usually over a period of 24 hours or more	Sudden especially with soluble insulin
DEHYDRATION	Marked with dry skin parched tongue and lowered eye ball tension	No signs of dehydration Moist skin often sweating Tongue moist Eye ball tension normal
CARDIOVASCULAR COLLAPSE	Usually marked with rapid thready pulse and lowered blood pressure	Usually a full bounding pulse and normal blood pressure
RESPIRATION	Characteristic Kussmaul breathing (air hunger) with smell of acetone in breath	Often quiet respirations but may be stertorous if coma is deep
REFLEXES	Often absent with flexor plantar responses	Usually brisk with extensor plantar responses Muscular twitchings and epileptiform seizure common
URINE	Heavy glycosuria acetonuria and often albuminuria Low urinary chloride level	Sugar free—certainly on ½ hourly collection after coming under observation Usually no acetone and normal urinary chloride level
BLOOD SUGAR	Raised 300–400 mg per 100 ml or more	Lowered 60 mg per 100 ml or lower
DEPTH OF COMA	Except in advanced cases patient usually rousable	Coma often deep

Spontaneous Hypoglycaemia

Any consideration of hypoglycaemia would be incomplete without including a brief reference to causes of hypoglycaemia other than those due directly to the administration of exogenous insulin. Thus there are many causes of endogenous hypoglycaemia and the more important are summarized in Table 2 and the subject has been fully reviewed by Conn and Seltzer (1955).

Table 2

I *Organic Hyperinsulinism*
  (1) Pancreatic islet cell adenoma
  (2) Pancreatic islet cell carcinoma
  (3) Generalized hyperplasia and hypertrophy of the islet cells of langerhans
II *Functional Hypoglycaemia*
III *Alimentary Hypoglycaemia*
  (1) After gastroenterostomy
  (2) After partial or total gastrectomy } Due to rapid intestinal absorption
IV *Hepatic Disease*
  E g severe hepatitis cirrhosis
V *Anterior Pituitary Hypofunction* due to any cause e g hypophysectomy Simmond s disease etc
VI *Adrenocortical Hypofunction* due to any cause e g adrenalectomy Addison s disease sudden withdrawal of Cortisone therapy
VII *Renal Glycosuria*
VIII *Idiopathic Spontaneous Hypoglycaemia of Infancy*

From this table it is clear that hypoglycaemia may often be a manifestation of serious metabolic or endocrine disease. In these cases the primary condition is likely to manifest itself by other symptoms and signs and diagnosis should present no problem. In the case however of organic hyperinsulinism due to adenomatous carcinomatous or other hyperplastic changes in the islet cells and in the case of functional hyperinsulinism the presenting symptoms are usually due to hypoglycaemia and it is important and may be diffi

cult to differentiate between cases of organic and functional hyperinsulinism

Organic Hyperinsulinism

This is a rare condition and when it occurs is usually due to a functioning islet cell adenoma Crain and Thorn (1949) reviewed 258 cases of organic hyperinsulinism from the literature They found an equal sex incidence and the tumours occurred at any age but predominantly from the 4th–6th decade Only 10 per cent of the cases showed any evidence of malignant change and diffuse hyperplasia was rare the majority of cases being due to single islet cell adenomata although multiple tumours were relatively frequent

The presenting symptoms are often bizarre and the patient is often thought to be suffering from an anxiety state a large number of the cases being referred to psychiatrists

Thus unexplained sweating tremor and syncopal attacks are often thought to have a psychogenic origin and it may only be when the patient has some more dramatic incident such as an epileptiform attack or a period of prolonged coma that the true diagnosis is suspected and confirmed by fasting the patient and if necessary for up to 72 hours when the blood sugar will be found to have fallen to 50 mg per 100 ml or less (Crain and Thorn 1949) and the patient's symptoms will be reproduced Whipple (1942) writes The syndrome associated with islet cell tumours must present the following essential triad—attacks of central nervous system disorder—motor vasomotor or psychic—coming on during the fasting state fasting blood sugar levels of 50 mg per 100 cc or less and immediate recovery from these attacks on the administration of glucose by mouth or by vein Unless this triad is present the diagnosis of a tumour requiring surgery should not be made

The glucose tolerance test is of little value in making a diagnosis of organic hyperinsulinism but Kelly (1956) has suggested that plasma insulin assays would be of great value in this respect

Once the diagnosis has been made it is essential to explore

the pancreas and it is important to stress that the search must be thorough as the tumour may be small

A case history is given as an illustration

J M age 42 a Latvian and machine fitter by trade was admitted to the King Edward VII Hospital Windsor in March 1956 He had flu in March 1955 for which he was in bed for one week With this he had a high temperature and one episode of confusion lasting for five minutes when he tried to go outside and had to be locked in his room Apart from that he was completely normal mentally during this illness

Three weeks later he began to get attacks of weakness in both legs which came on usually quite suddenly when he was cycling home—a seven mile journey—and tended to occur towards the end of the week The weakness was so marked that he had to get off his bicycle and wait by the side of the road for 1 1½ hours before being abl to resume his journey During these attacks he had no pain in his legs and no trouble with his arms he could speak normally and claims that he was mentally completely alert

These attacks continued for two months and then in May 1955 *were superseded by a different sort of attack He com* plained one Sunday morning of weakness of his legs and remained in bed His wife says that he was then quite rational but when she returned in the evening she found that he was still in bed and was unable to rouse him A few hours later he came round but did not recognize her for a further two hours when he again appeared completely normal men tally He had not bitten his tongue nor been incontinent during this period

These sleeping attacks were usually ushered in by a complaint of weakness of the legs in going to bed on Saturday night and ended by his waking up at 3 p m on the following Sunday afternoon his wife having been unable to rouse him in the meantime These episodes continued regularly at week ends for about five weeks and then stopped

He then remained completely well until November 1955 when the sleeps recurred at first at fortnightly intervals and always at week ends In December he had an episode of weakness of his legs at work and since then the attacks of

weakness now followed (always) by sleeping became more frequent For the two months before his admission on the 24th March 1956 he had been having about three attacks a week It was then noticed that they tended to come on after exercise and that before he became gradually drowsy his concentration became poor and his speech irrational and slurred At this point in the attack it was noticed that rest or food improved him and that the slightest exertion such as moving from his chair or even talking made him worse The periods of unconsciousness were lasting longer 20–24 hours and during the three most recent attacks he had been seen to shake all four limbs violently and bite his tongue and four hours before admission he had been incontinent of urine The attack in which he was admitted was the longest he had had and when he came in he had been unconscious for 40 hours

He had had no headache no vomiting and no other trouble with his limbs or speech and apart from the attacks he had remained completely normal mentally There had been no visual disturbance and apart from these episodes he had never had anything resembling a fit His appetite was good and his weight steady He had no chest or abdominal symptoms and between attacks he felt quite well and was then physically quite normally strong He had had no sphincter disturbances

Past History His wife said that he had had a brain illness at the age of four years but no details were known He had had no operations and had had no head injury as far as was known and no serious illness He came to England from Germany in 1947 having been in Latvia before then He had never travelled outside Europe

On admission on 24th March 1956 he was comatose restless and moving all limbs equally and with considerable power and was responsive only to pain He was pale but not sweating his skin was dry his tongue was clean and moist *He was not clinically dehydrated* There was no neck stiffness nor Kernig s sign His pupils were equal but not dilated and reacted briskly to light There were occasional lateral nystagmoid jerks to right and left fundi normal corneal reflexes equal and brisk There was no facial asymmetry

The tone in his limbs was equal and slightly decreased Tendon reflexes were all present but slightly increased in the right leg the abdominals were absent and both plantar responses were extensor Pulse 80/min regular and full B/P 110/70 Heart lungs and abdomen—N A D Temperature—axillary 99

Shortly after admission he had a generalized convulsive attack in which there was jerking of all four limbs cyanosis and bladder incontinence His blood sugar was found to be 13 mg per 100 ml and he was given 75 G glucose i/v without change in his state except that he became more violent His blood sugar 1 hour later was 235 mg per 100 ml Six hours after admission he was confused but accessible and was able to take fluids by mouth On the following morning he had an attack of sweating and became violent and confused his blood sugar at that point having fallen to 20 mg per 100 ml He was from that time on given a normal diet with glucose ½ oz (14 G) per hour by mouth

During the next few days his requirements of glucose steadily increased and it was felt that it would be unwise to pursue any further investigations because of possible irreversible damage to the C N S for this reason a glucose tolerance curve was not attempted His plantar responses were still extensor and five days after admission he had still not regained voluntary control of his bladder

On 30th March 1956 despite his having been given 10 G Dextrose per hour i/v during the night his blood sugar at 9 30 a m was 26 mg per 100 ml He was therefore given 20 G Dextrose per hour which raised his blood sugar to only 54 mg per 100 ml by 1 45 p m

Operation 30th March 1956 The pancreas was explored and a round tumour a little more than 1 cm in diameter was found in the head of the pancreas and excised

Within five days of operation he appeared to have returned to normal mental alertness he had full control of his bladder and his plantar responses were flexor He made an uninterrupted post operative recovery and was discharged on 14th April 1956

Histology Adenoma of the islets of Langerhan

Observations In view of the curious week end periodicity of these "sleeps" the question of his diet and exercise on Saturdays was gone into During the week his work is heavy On Saturday afternoons he does very little physical work spending his time in the garden Tea and supper on Saturdays are apparently virtually the same in amount and timing as on week days The weakness of his legs usually came on at about 7 0 p m on Saturday evenings i e ½–1 hour after supper This timing and in particular the fact that his "sleeps" would begin before he had had any break fast on Sundays was more suggestive of an organic than of a functional i e "reactive" hyperinsulinism and the progres sion in frequency and severity of the attacks coupled with the extremely low blood sugar levels found after admission made an organic cause almost certain An attempt to assess his response to a provocative (low calorie) diet had to be aban doned because even on a normal diet but without added glucose his blood sugar fell to dangerous levels There was nothing to suggest liver damage either clinically or bio chemically and exploration of his pancreas was therefore considered to be essential

FUNCTIONAL HYPERINSULINISM

This condition is not characterized by an abnormally low fasting blood sugar level but after a glucose meal the blood sugar level rises normally but falls to hypoglycaemic levels between the 2nd and 4th hours and only slowly returns to normal During the appropriate hypoglycaemic phase the patient has mild symptoms but loss of consciousness is rare

The treatment for patients with this condition is to advise a spaced carbohydrate diet in which they are told not to take a large carbohydrate meal which would produce reactive hypoglycaemia but they may be advised to use glucose to correct their symptoms should they occur Protein and fat may be taken in average amounts Instead of referring to this as a functional condition Prunty (1944) has suggested that the syndrome is better described as being due to reactive hyperinsulinism

Idiopathic Spontaneous Hypoglycaemia of Infancy

Severe persistent hypoglycaemia of unknown cause has been described in otherwise healthy infants McQuarrie (1954) in reviewing 40 cases of hypoglycaemia found 25 idiopathic cases Of these 84 per cent were under two years of age at the time of onset of distinct manifestations of hypoglycaemia and 76 per cent were between the ages of 3 to 18 months 18 were males and 7 were females There was a high familial incidence (44 per cent) while the family histories of the other patients indicate the probable excurrence of the syndrome in a previous generation The absence of physical stigmata and normal responses to all special tests except those immediately related to glucose and insulin tolerance characterize the cases of idiopathic infantile hypoglycaemia McQuarrie (1954) found that no genuine case so far tested failed to respond favourably to treatment with corticotrophin

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CHAPTER VIII

PRACTICAL PROCEDURES

by D H NOBES *and* J LISTER

I Urine Analysis

1 **Tests for Glucose** Since routine urine testing plays an invaluable part in the diagnosis of diabetes simple screening tests are required Any of the well known copper reduction tests—Fehling s Benedict s Clinitest may be used but in addition to glucose they all detect other substances which are *of no importance in connection with* diabetes Two new enzyme tests—Clinistix and Tes Tape which are specific for glucose in urine have now become available These are ideal screening tests because of their simplicity but as they are only reliable qualitative tests Baron and Newman (1958) Davies and Paley (1957) Dumm and Shipley (1946) Folin and Wu (1920) another test such as Clinitest or Benedict s test should be used to determine the amount of glucose present on those urines positive to one of the enzyme tests

As an aid to diabetic management a semi quantitative test is necessary Clinitest is the most convenient test available both for use in the clinic and by the patient

Qualitative Tests

(a) Clinistix Reagent Strips

Dip test end of Clinistix in urine and remove Alternatively the test end may be placed in the urine stream momentarily or moistened with a drop of urine

Negative No blue colour develops

Positive Moistened end turns blue

When glucose is present a blue colour normally appears in less than a minute but occasionally may be delayed a minute or so depending on the nature of the urine

(b) *Tes Tape Urine Su ar Test Tape—Lilly*

Remove approximately 1½ of Tes Tape and dip in specimen Remove and wait 1 minute then immediately compare darkest area with Tes-Tape colour chart

Negative In the absence of glucose the tape remains yellow

Positive The tape will change colour ranging from faint green to deep blue depending on the amount of glucose present

Caution Both of the enzyme tests *Clinistix* and *Tes Tape* are based on very sensitive enzyme reactions and care must be taken to avoid contamination of the sticks and tape with glucose or other chemicals The impregnated material should not be handled with the fingers as they may have traces of gluco e on them

Clinistix and *Tes Tape* are both specific for glucose but are not suitable for quantitative use due to the influence of pH temperature and the presence of antagonistic substances such as ascorbic acid Baron and Newman (1958) Davies and Paley (1957) Dumm and Shipley (1946)

Quantitative Tests

(a) *Clinitest Reagent Tablets*

Place 5 drops (0 25 ml) of urine into the test tube using the standardised *Clinitest* dropper

Rinse dropper and add 10 drops of water

Drop one *Clinitest* tablet into the test tube

Watch while the reaction takes place

Do not shake test tube during the reaction nor for 15 seconds after the boiling inside the test tube has stopped After the 15 seconds waiting period shake tube gently and compare with the standard *Clinitest* colour scale

Negative The fluid will be blue at the end of the 15 second waiting period All shades of blue are negati e The whitish sediment that may form has no bearing on the test

Positive The fluid will change colour and the more sugar present the more rapidly will it occur The amount present is determined by com

paring the tube with the colour scale at the end of the 15 second waiting period and *any change after this period should be disregarded*

An amount of sugar over 2 per cent causes rapid colour changes which pass through all shades including the orange and finally turns to a dark greenish brown which should not be confused with any colour on the chart

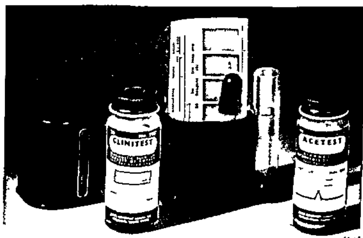


FIG VIII 1 —Clinitest reagents

Providing the reaction is watched carefully there should be no difficulty in noticing if the colour *passes through orange* to this dark brown shade in which case the result should be reported as over 2 per cent without reference to the colour scale See Fig VIII 1

(b) *Benedict s Test*

Put into a test tube

5 0 ml *Benedict s Qualitative Reagent*

0 5 ml Urine

Place tube in vigorously boiling water for 5 minutes or *boil* over a flame for 2 minutes.

In the presence of a reducing substance (glucose in diabetes) a yellow or red precipitate of cuprous oxide is formed—the final colour depending on the amount of glucose present.

Greenish blue	0.1–0.2%
Yellowish green	0.5%
Brown	1.0%
Reddish brown	2.0%
Bright red	More than 2.0%

Note. It is important to adhere to the above quantities and time of boiling particularly if the results are to be used to assist in the control of a diabetic patient.

2. **Tests for Ketones.** It is important to recognise the limitations of the available tests. It is generally accepted that the Rothera test is somewhat too sensitive and frequently gives positive reactions to low levels of ketonuria of no clinical significance. In contrast to this the Gerhardt ferric chloride test is not sensitive enough to be used alone. It also had the disadvantage that the urine of patients receiving many commonly administered drugs gives a similar reaction. *Acetest* tablets are a fair compromise as their sensitivity is intermediate between that of the Rothera and Gerhardt tests (Frazer 1958). A "trace" reaction with *Acetest* usually denotes ketonuria of clinical significance and a "moderate" or "strongly positive" result indicates severe diabetic ketosis (Himsworth 1936). If however it is desired to detect the faintest ketonuria Rothera's test is the most sensitive.

(a) *Acetest Reagent Tablets*

A tablet is placed on a clean white surface and one drop of urine is placed on top of it. At the end of 30 seconds the purple colour which develops in the presence of ketones is compared with the *Acetest* colour chart and the result recorded as "trace", "moderate" or "strongly positive".

In common with all nitroprusside reactions for ketones the colour will continue to develop for several minutes. For

paring the tube with the colour scale at the end of the 15 second waiting period and *any change after this period should be disregarded*

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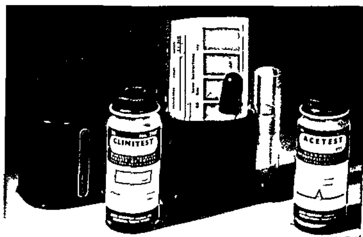


FIG VIII 1 —Clinitest reagents

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(*b*) *Benedict s Test*

Put into a test tube

5 0 ml *Benedict s Qualitative Reagent*
0 5 ml Urine

to the decomposition of this compound to acetone which does not react with ferric chloride

3 Tests for Protein

(a) Salicylsulphonic Acid Test

Place about 5 0 ml of urine into a test tube (filtered if cloudy)

Add about 0 5 ml 25% salicylsulphonic acid

A white precipitate which may vary from a very faint haze to a heavy turbidity will occur in the presence of protein

It is important that the approximate quantities of urine and reagent are adhered to as the addition of insufficient salicylsulphonic acid to a urine which is very alkaline could result in a false negative test

Although a very reliable test false positives may occasionally occur due to the presence of uric acid or radio opaque materials such as Uroselectan

(b) Boiling and Acetic Acid Test

Fill a test tube three quarters full with clear urine (cloudy urine must be filtered before testing)

Incline the tube at an angle and boil the upper ½ portion by rotating the tube carefully in a small flame Turbidity indicates the presence of protein or phosphates

Add one drop of 33% acetic acid or equivalent quantity of a weaker strength and boil again momentarily Any remaining turbidity indicates the presence of protein

It is important that excess of acetic acid is not added as if the urine is itself acid small amounts of protein may be missed due to its conversion into acid metaprotein on boiling On the other hand if the original reaction of the urine is very alkaline it is advisable to make it slightly acid before carrying out this test as even large amounts of protein can be missed if the urine is still alkaline when boiled

(c) Albustix Reagent Strips

Dip test end of Albustix in urine and remove Alternatively the test end may be placed in the urine stream momentarily or moistened with a drop of urine

Negative No colour change develops

Positive Moistened end turns green to blue-green immediately The stick may be compared with the colour scale provided and the result reported as negative trace moderate or strong ✓

As the colour reaction is not affected by the turbidity of the urine it is not necessary to filter before making a test Albustix has approximately the same sensitivity as the salicylsulphonic acid and boiling tests (Hunt *et al* 1956 King and Wootton 1956)

II Blood Analysis

1 *Blood Sugar Estimation (Glucose)* Numerous methods are available for the estimation of total reducing substances and for true glucose The following are selected for their simplicity and convenience for routine use

(*a*) *Method—Folin and Wu* (*Micro method*) (Leonard 1957) —Total Reducing Substances

Procedure Into a small test tube 3 × ½ place the following

3 5 ml distilled water
0 1 ml blood
0 2 ml 10% sodium tungstate
0 2 ml ⅔ N sulphuric acid

Mix and stand 10 minutes until protein precipitate clumps then filter or centrifuge

Into a Folin tube place
2 0 ml blood filtrate
2 0 ml alkaline copper reagent

Standards

(A) Into a Folin tube place
2 0 ml 0 005% glucose
2 0 ml alkaline copper reagent

(B) 1 0 ml distilled water
1 0 ml 0 005% glucose
2 0 ml alkaline copper reagent

In each case mix and place in a boiling water bath for

exactly 6 minutes Cool for one or two minutes and do not shake

Add 2 0 ml phosphomolybdic acid reagent dilute with water to the 12 5 ml mark and mix by inversion

Allow to stand for a few moments for bubbles to rise and then compare in visual or photoelectric colorimeter using a red or orange filter

Calculation

Standard (A)—

$$\frac{\text{Reading of Test}}{\text{Reading of Standard}} \times 100 = \text{mg sugar per 100 ml blood}$$

Standard (B)—

$$\frac{\text{Reading of Test}}{\text{Reading of Standard}} \times 50 = \text{mg sugar per 100 ml blood}$$

Reagents

10% w v sodium tungstate

⅔ N sulphuric acid

Alkaline Copper Reagent Dissolve 40 g anhydrous sodium carbonate in 400 ml of water Transfer to a 1 litre flask 7 5 g of tartaric acid and wait until this has dissolved Transfer quantitatively to the flask 4 5 g crystalline copper sulphate which has been dissolved in about 100 ml of water Mix and make up to volume

Phosphomolybdic Acid Reagent Dissolve 35 g molybdic acid and 5 g sodium sulphate in 250 ml of 2N NaOH and boil for 30 minutes Add water to 350 ml and 125 ml of 89% phosphoric acid (sp gr 1 75) dilute to 500 ml

Stock Glucose Solutions Dissolve 0 1 g pure anhydrous glucose in saturated benzoic acid solution (0 3%) to volume of 100 ml This is a permanent standard

Standard Glucose Solutions Dilute 1 0 and 2 5 ml of the stock glucose solution with isotonic sodium sulphate copper sulphate to 100 ml giving standards of 0 02 and 0 05 mg per 2 ml (=80 mg and 200 mg glucose per 100 ml of blood) It is recommended that this be stored in a refrigerator

Negative No colour change develops

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2 0 ml blood filtrate
2 0 ml alkaline copper reagent

Standards

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2 0 ml 0 005% glucose
2 0 ml alkaline copper reagent

(B) 1 0 ml distilled water
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2 0 ml alkaline copper reagent

In each case mix and place in a boiling water bath for

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Add 2 0 ml phosphomolybdic acid reagent dilute with water to the 12 5 ml mark and mix by inversion Allow to stand for a few moments for bubbles to rise and then compare in visual or photoelectric colorimeter using a red or orange filter

Calculation

Standard (A)—

$$\frac{\text{Reading of Test}}{\text{Reading of Standard}} \times 100 = \text{mg sugar per 100 ml blood}$$

Standard (B)—

$$\frac{\text{Reading of Test}}{\text{Reading of Standard}} \times 50 = \text{mg sugar per 100 ml blood}$$

Reagents

10% w v sodium tungstate

$\frac{2}{3}$ N sulphuric acid

Alkaline Copper Reagent Dissolve 40 g anhydrous sodium carbonate in 400 ml of water Transfer to a 1 litre flask 7 5 g of tartaric acid and wait until this has dissolved Transfer quantitatively to the flask 4 5 g crystalline copper sulphate which has been dissolved in about 100 ml of water Mix and make up to volume

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(b) *Asatoor and King Method* (Modified) (Moss 1957)—True Glucose

Procedure Into a conical centrifuge tube place the following

0 05 ml blood

3 9 ml Isotonic sodium sulphate copper sulphate *solution*

0 05 ml sodium tungstate

Shake well and centrifuge

Into a test tube ⅝ in diameter place

2 0 ml of supernatent fluid

2 0 ml of modified Harding B reagent

Standards Into similar tubes place

(A) 2 0 ml *of 80 mg % glucose standard*

2 0 ml of Modified Harding B reagent

(B) *2 0 ml of 200 mg % glucose standard*

2 0 ml Modified Harding B reagent

The tubes are stoppered with cotton wool and placed in a boiling water bath for exactly 10 minutes *Cool* immediately and add

6 ml of arsenomolybdic acid reagent *or* 6 ml of phosphomolybdic acid reagent

5 ml of water

Dilute with an additional 5 or 10 ml of water when glucose concentration is high

Compare in visual or photoelectric colorimeter using red or orange filter

Calculation

Standard (A)—

$$\frac{\text{Reading of Test}}{\text{Reading of Standard}} \times 80 = \text{mg glucose per 100 ml blood}$$

Standard (B)—

$$\frac{\text{Reading of Test}}{\text{Reading of Standard}} \times 200 = \text{mg glucose per 100 ml blood}$$

Reagents

Modified Harding Solution B (half strength) Dissolve

50 g $NaHCO_3$ in a beaker with about 700 ml of distilled water Stir in 40 g anhydrous Na_2CO_3—add 36 8 g potassium oxalate in 120 ml of warm water Add a solution of 24 g sodium potassium tartrate in about 100 ml of water Pour into a 2 litre volumetric flask up to the mark and shake well

Phosphomolybdic Acid Reagent Dissolve 35 g molybdic acid and 5 g sodium sulphate in 250 ml of 2N NaOH and boil for 30 minutes Add water to 350 ml and 125 ml of 89% phosphoric acid (sp gr 1 75) dilute to 500 ml

Arsenomolybdic Acid Reagent Dissolve 25 g ammonium molybdate in 450 ml of water Add 21 ml conc sulphuric acid mix and then add 3 g of sodium arsenate


($Na_2HAsO_4\ 7H_2O$)

dissolved in 25 ml of water Keep mixture in 37 bath for 2 days For use dilute one part reagent with two parts water A R chemicals should be used for the reagent

Isotonic Sodium Sulphate/Copper Sulphate Solution 320 ml of 3% sodium sulphate ($Na_2SO_4\ 10H_2O$) plus 30 ml of 7% $CuSO_4\ 5H_2O$

Sodium Tungstate 10 g per 100 ml kept in a waxed bottle

Stock Glucose Solution Dissolve 0 1 g pure anhydrous glucose in saturated benzoic acid solution (0 3%) to volume of 100 ml This is a permanent standard

Standard Glucose Solutions Dilute 1 0 and 2 5 ml of the stock glucose solution with isotonic sodium sulphate/copper sulphate to 100 ml giving standards of 0 02 and 0 05 mg per 2 ml (=80 mg and 200 mg glucose per 100 ml of blood) It is recommended that this be stored in a refrigerator

(c) *Dextrotest*

This is a new method available in the United States (Nabarro 1958 Nash *et al* 1954) for the approximate estimation of total reducing substances and has the special advantage of providing a result within 5 minutes of collecting the blood

All reagents and simple equipment required for performing a test are provided in the kit

Procedure

Place water in test tube provided to 2 ml mark and add *the protein precipitant tablet P*

After tablet has dissolved add 1 ml blood invert and shake to mix thoroughly

Immediately pour mixture through dry filter paper and collect filtrate to 1 ml mark in second tube

Add copper reagent tablets to filtrate Do not shake while boiling but after boiling stops shake tube gently 3 or 4 times

Wait 30 seconds and compare with colour scale which indicates 100 150 and 200 mg per 100 ml blood It is possible with experience to make estimations between *the colours on the scale*

If the concentration of sugar is more than 200 mg per cent the test may be repeated using 0 5 ml of blood and *2 5 ml of water or the protein free filtrate may be diluted* with an equal quantity of water The result obtained with either of these modified techniques is multiplied by two to obtain the glucose concentration per 100 ml of blood

3 Glucose Tolerance Test

Preparation of Patient

The patient is allowed nothing to eat and drink overnight but a cup of tea without sugar may be allowed early on the morning of the test

Procedure It is usual for glucose tolerance tests to be carried out on capillary blood

Collect specimen of blood and urine

Give 50 g of glucose dissolved in about 200-250 ml water flavoured if desired An additional glass of water may be given if required

At half hourly intervals after the glucose is given speci*mens of blood are taken up to 2 hours*

Samples of urine are collected 1 hour and 2 hours after the glucose dose

Glucose estimations are *carried out on the five* blood

specimens and these are plotted on a graph against the time of collection of the specimens The three urine specimens are tested for glucose and ketones and the results also marked on the graph

Doses of 100 g of glucose may be given but appear to have little advantage over the test employing 50 g

For children 1 g of glucose is given per 3 lbs of body weight

4 Insulin/Glucose Tolerance Test

Procedure

Collect specimen of blood

Inject intravenously 0 1 unit insulin per kg of body weight

Collect second specimen of blood half an hour after injection

0 8 g glucose per kg body weight is given by mouth immediately after collection of 30 minute blood specimen

Further blood specimens are collected 1 hour 1½ hours 2 hours and 3 hours after the insulin injection

It is usual to express the results as percentages of the initial blood sugar level

5 Blood Ketones

Accurate methods for the determination of blood ketones are rarely employed clinically but valuable information may be obtained from the application of simple nitroprusside tests

(a) *Dumm and Shipley Test* (Schmidt 1937)

A powder containing the following ingredients is used

1 g sodium nitroprusside (finely ground)
20 g ammonium sulphate
20 g sodium carbonate anhydrous

Mix thoroughly without grinding If kept dry the powder should remain stable for about a year

Procedure

A drop of serum is placed on to a small pinch of the powder about 5 mm in diameter

If this test is positive the serum is diluted one in two and the test repeated

If still positive dilutions are continued until no colour reaction is obtained

The dilution is multiplied by 10 to obtain the very approximate concentration of acetone and acetoacetic acid in mg per 100 ml

(*b*) *Acetest Reagent Tablets*

One drop of serum is placed on to an Acetest tablet and the colour read at 30 seconds

In the presence of a clinically significant increase in ketones the familiar pinkish purple colour will occur and a guide to the concentration may be obtained by comparison with the colour scale provided with the tablets

III Insulin Administration

Strengths of Insulin Preparations Insulin is standardized in units and the strength of an insulin preparation is expressed in terms of units per ml Soluble insulin is supplied in strengths of 20 40 and 80 units per ml while the other insulin preparations are supplied in strengths of 40 and 80 units per ml When large doses are being prescribed the 80 unit per ml strength is often used as it allows a high dosage to be injected in a smaller volume

It is vital for the patient to understand the dosage system and for the actual dose to be prescribed in units The standard colour system adopted by the British Insulin Manufacturers for identifying the different types of insulin should make mistakes avoidable and apart from these colours every package bears printed details of its contents

Storage of Insulin Insulin should be stored in a cool place but should never be allowed to freeze Insulin should not be used after its expiry date

The Insulin Syringe The most satisfactory syringe available for diabetics in this country is the British Standard Insulin Syringe (B S 1619) It is made in 1 ml and 2 ml sizes and takes Luer type needles It is specially designed for diabetics and for the convenient measurement of the dose in units The word unit does not appear on the B S 1619

insulin syringe since the number of units measured by withdrawing the plunger to any one point depends upon the strength of insulin being used The syringe is therefore marked into twenty divisions for each unit so that 5 marks on the syringe will measure 5 units of 20 unit strength insulin 10 units of 40 unit strength or 20 units of 80 unit strength (Fig VIII 2) Provided the dose is always prescribed in units and the strength of the preparation is clearly understood there should be no possibility of confusion

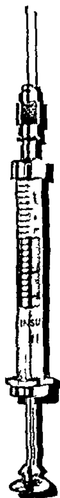


FIG VIII 2—The British Standard Insulin Syringe (BS 1619)

Care of Syringe and Needles Most patients sterilize their syringes either by boiling them or by immersing them in spirit

Sterilization by Boiling The dismantled syringe the needle and a pair of forceps are first placed in a saucepan of cold water which is then brought to the boil and boiled for not less than five minutes Afterwards the water is gently poured away the saucepan lid being held to retain the apparatus The apparatus is then left to cool in the covered saucepan the syringe itself is reassembled with the sterile forceps or with clean dry fingers and the needle reaffixed with the sterile forceps

Sterilization with Spirit The most effective strength of alcohol is best prepared by diluting *four* parts of industrial spirit* with not more than *one* part of boiled water The spirit freshly taken from a stoppered bottle should be mixed with the water in a suitable shallow vessel large enough to hold the dismantled syringe Every few days the mixture must be changed

After use the syringe itself is first washed

* Industrial spirit is preferable to surgical spirit for sterilization of syringes

clean in tap water the needle is reattached and spirit mixture is drawn up several times to wet the inside of the needle thoroughly *The syringe is then dismantled and* together with the needle totally submerged in the spirit mixture in the vessel This is then covered over and the syringe and needle are left immersed until they are next required

When needed next the syringe parts are lifted from the vessel with forceps sterilized by partial immersion in the spirit for at least five minutes excess liquid is shaken off and the parts are reassembled with the forceps or with clean dry fingers The forceps are then used to lift the needle from the vessel and to reattach it to the barrel

Needle Size The best size of needle for making injections of insulin is from No 17 to No 20 Needles should be kept sharp With practice they can be sharpened on a fine razor stone or they can be sharpened by experts

Insulin Injection

Most diabetics who need insulin should make their own injections

Injection Sites The best sites for injecting insulin are the outer areas of the thighs the sides of the abdomen and (with practice) the outer areas of the upper arms Injections may in fact be made in any convenient region of the body where the skin is loose No two injections should be made close to each other within a period of at least a week The site of injection should be changed from time to time it is a good plan to change from one thigh to the other or from one side of the abdomen to the other at regular weekly or fortnightly intervals

Measuring the Dose All types of insulin except soluble insulin and globin zinc insulin which are clear solutions must be shaken in the bottle before use The insulin zinc suspensions should be shaken well protamine zinc insulin and isophane insulin should be shaken only gently The cap from an insulin bottle should never be removed To withdraw a dose the following method should be used

(1) After shaking the bottle (if the type of insulin needs it) clean the cap with cotton wool soaked in an antiseptic
(2) Expel any spirit from the syringe and needle by working the plunger up and down
(3) Raise the plunger to the mark on the barrel corresponding to the dose required
(4) Holding the bottle at a convenient angle push the needle through the rubber cap
(5) Turn the bottle upside down Push the plunger to inject the air in the syringe into the bottle (If you omit to do this you will have difficulty in withdrawing the dose as a partial vacuum will form inside the bottle)
(6) Make sure that the needle tip is well below the surface of the liquid in the inverted bottle
(7) Pull the plunger down to draw in insulin Draw in slightly more insulin than required Push the plunger slightly to expel any trapped air bubbles Measure the dose exactly and remove the syringe and needle from the bottle cap which will then reseal itself

Mixed Doses When a mixed dose of two insulins is prescribed (i e soluble insulin and protamine zinc insulin soluble insulin and globin zinc insulin soluble insulin and isophane insulin or a mixture of two insulin zinc suspensions) these should be mixed in the syringe

Before preparing a mixed dose a little air should be injected into one of the two bottles The correct amount of insulin should then be withdrawn from the other bottle as described above the needle should be re inserted into the first bottle and the correct amount of insulin withdrawn from that

When soluble insulin is included in the dose it must always be measured *before* the other insulin This means that the preliminary injection of air must be made into the bottle containing protamine zinc globin zinc or isophane insulin

Injecting the Dose With an insulin zinc suspension or a mixture of two insulin zinc suspensions the syringe should

be gently rotated in the hands immediately before the injection

To make an injection of insulin is not difficult

(1) Cleanse the skin where the injection will be made using a mild antiseptic
(2) Holding the syringe by its barrel with one hand pinch up the skin with the fingers of the other hand
(3) Thrust the needle in along the fold
(4) Pull back the plunger without moving the needle to see if any blood enters the syringe (This very seldom happens but if it does do so you must withdraw the needle and make another puncture)
(5) Keeping the syringe steady press the plunger down to inject the insulin
(6) Withdraw the needle along the path of entry and press down firmly on the point of puncture with cotton wool for about 15 seconds (Fig VIII 3)



FIG VIII 3 —Injecting the dose

Alternatively the injection can be made by an injector gun The insulin is drawn up in the syringe as before the syringe attached to the gun and by pulling the trigger

insulin is injected at the correct depth in the skin Fig VIII 4 illustrates the Palmer injector gun *

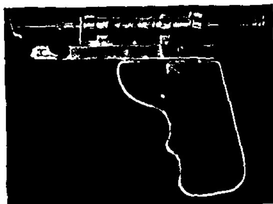


FIG VIII 4—Palmer jector gun

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* Available from Palmer Injectors Ltd Fort William

PART II

COMPLICATIONS AND ASSOCIATED CONDITIONS

INTRODUCTION

THE increased life span which insulin has granted to diabetics has also made them an ideal population in whom to study the natural history of the disease As groups of diabetic patients are observed over the years either in practice or in diabetic clinics so the evolution of the fully developed syndrome of diabetes can be followed

Severe diabetic ketosis should now be an uncommon complication in the known diabetic and death from diabetic coma should be a rarity Hypoglycaemia is a complication of the treatment of diabetes but provided the circumstances in which it is likely to occur are understood and correct treatment is quickly instituted either by the patient or his doctor the consequences should rarely be serious

On the other hand there are a number of complications which appear to be related either to the duration of the diabetes or to the degree of diabetic control or to both of these factors In particular diabetics are liable to develop vascular degenerative disease This affects the coronary arteries the peripheral arteries and there is also what appears to be a specific type of diabetic vascular disease affecting the retinal and renal vessels A number of neurological complications are also recognized and have been grouped under the heading of diabetic neuropathy and it is now recognized that those lesions of the limbs which were formerly loosely described as diabetic gangrene may either be primarily vascular primarily neuropathic or due to a combination of both factors with or without superadded infection

Similarly the diabetic who comes for surgery may present a problem although the safety and efficiency of modern anaesthesia has greatly minimized the potential hazards involved so long as simple principles of treatment are fol

lowed In addition to these complications of diabetes there are a number of other conditions such as pregnancy and pulmonary tuberculosis which have to be considered as associated conditions because they may either modify or be modified by the diabetic state

These then are the aspects of diabetes which will be considered in the following chapters bearing in mind the fact that although diabetes is a lifelong condition the duty of the physician is to help the patient make it as little a disability as possible

CHAPTER IX

DIABETIC VASCULAR DISEASE

The most serious threat to the life of a diabetic to day results from cardiovascular degeneration In the Naunyn era of 1894–1914 diabetic coma caused the death of 61 per cent of diabetics and diabetic arteriosclerosis accounted for 15 per cent of deaths Joslin (1930) found that diabetic coma was only causing 11 per cent of diabetic deaths in his series while vascular disease was accounting for 50 per cent He also found that the longer the duration of the disease the greater was the incidence of arteriosclerosis and in cases of more than 30 y ars standing it was the cause of 68 per cent of deaths Later reviews have confirmed this high incidence of vascular disease in diabetics Rabinowitch Ritchie and McKee (1934) found an incidence of arteriosclerosis in 85 per cent of dia betics under 50 years of age who had been diabetic for more than 5 years Dolger (1946 1947) found that of 200 diabetics followed for 25 years none escaped degenerative vascular disease Further emphasis is given to the importance of the duration of the disease rather than the age of the patient as the determining factor in the development of vascular degeneration by the observations of Chute (1948) that even in juvenile diabetics who survive more than 15 years the incidence of such changes is high This tragic observation presents one of the greatest problems in the treatment of diabetes and Wilson Root and Marble (1951) found that of 247 young patients with severe diabetes of 10–34 years duration with onset at ages between 18 months and 30 years 25 per cent had manifestations of diabetic neuropathy

The pathology of diabetic vascular disease has been likened to an accelerated arteriosclerotic process together with vascular changes in the retinal and glomerular vessels which are almost specifically diabetic

The accelerated arteriosclerotic process may take the form of atherosclerosis with the laying down of intimal plaques of

atheroma Monkeberg s sclerosis with medial calcification in the vessels to the legs or of arteriolarsclerosis when the lesion chiefly affects the medium sized vessels and is then usually associated with some degree of hypertension The specific changes in the retinal and glomerular vessels are responsible for the development of diabetic retinopathy and nephropathy

It is clear that a variety of clinical pictures may result from such changes and they may frequently occur in the same patient It is however convenient to consider the more common conditions under the following headings

(1) Coronary artery disease
(2) Peripheral vascular disease
(3) Diabetic retinopathy
(4) Diabetic nephropathy
(5) Hypertension in diabetes

1 **Coronary Artery Disease** Many workers have shown that coronary artery disease occurs more frequently in diabetic than non diabetic persons It occurs at an early age in diabetics (Warren 1930) and also occurs equally in male and female patients although in non diabetics the incidence is in the ratio of 3 male to 1 female (Nathanson 1925) Autopsy studies have been carried out by many workers and have proved the high incidence of coronary artery disease Millard and Root (1948) reported on the state of the coronary vessels in 110 diabetic autopsies In 10 per cent of cases there was no macroscopic disease in 21 per cent there was sclerosis without narrowing in 34 per cent there was narrowing without occlusion and in the remaining 34 per cent there was actual occlusion present These workers emphasize that this incidence of 34 per cent coronary occlusion is more than six times as great as that encountered in non diabetics Using a special technique of injection combined with dissection Stearns Schlesinger and Rudy (1947) found some degree of arteriosclerosis in the coronary artery tree in every case they examined Root *et al* (1939) stated that cardiac infarction occurred 5 times as frequently in the diabetic as in the non diabetic

The outstanding clinical features of coronary artery disease in diabetics are that both frank cardiac occlusion and

angina of effort are observed almost as frequently in female patients as in males in contrast to the normal population and that symptoms of coronary artery disease are observed at an unusually early age in both sexes Routine electrocardiographic studies on diabetic patients have shown ischaemic changes in a high proportion of the cases Hepburn and Graham (1928) found that below the age of 50 19 4 per cent of tracings were abnormal but above that age the incidence of abnormal tracings rose to 51 7 per cent The majority of the abnormal *tracings showed T wave changes or abnormalities* in the QRS complex while bundle branch block or other evidence of intraventricular conduction defect was not uncommon

From the clinical viewpoint the management of a cardiac infarct in diabetics differs in no way from that in non diabetics and there is no contra indication to anticoagulant therapy In the early stages however some degree of ketosis is the rule and occasionally precoma may develop The management of this complication demands its own treatment but it is important to avoid hypoglycaemia in correcting ketosis because there is a tendency for hypoglycaemia to aggravate myocardial ischaemia (Murdock 1951) and any intravenous therapy must be carried out with the utmost caution because of the danger of precipitating cardiac failure

The importance of myocardial infarction as a cause of death in diabetics and as a *factor influencing the expectation* of life in diabetics has been stressed by Marble (1955) who found that of 102 diabetic patients admitted to the New England Deaconess Hospital with acute myocardial infarction 60 8 per cent died within the first 60 days Bradley and Bryfogle (1956) found that coronary artery disease was accounting for nearly one half of all deaths in diabetic patients and of their cases 57 8 per cent died after the first attack Thus the diabetic with a cardiac infarct has a prognosis similar to that of poor risk cases in the general population The late survival rate is also poor and Bradley and Bryfogle (1956) found that only 20 per cent of diabetic patients survived 5 years and only 3 6 per cent survived 10 years after their initial attack

2 Peripheral Vascular Disease In reviewing autopsies on 175 diabetic patients Root and Sharkey (1936A) found that the premature arteriosclerosis chiefly affected the muscular arteries under greatest strain namely the coronary arteries the aorta and the arteries of the legs These findings were in accord with the much earlier clinical observations of Heitz (1924) that coronary artery disease intermittent claudication and diabetes were frequently present in the same patient Intermittent claudication is however a much less common manifestation of peripheral vascular disease in diabetics than gangrene of the extremities Intermittent claudication affecting the calf is in most cases due to obstruction of the femoral or popliteal arteries gangrene is more often due to lesions in the more peripheral vessels

It is not easy to lay down criteria which may be taken to indicate the presence of peripheral vascular disease The absence of pulsation in the dorsalis pedes artery is often considered pathological but Silverman (1946) found that the dorsalis pedes pulses were absent in 13 per cent of otherwise normal young men

Semple (1953) has suggested that the presence of one or more of the following criteria may be taken as evidence of peripheral vascular disease

(1) A history of typical intermittent claudication or gangrene
(2) Disappearance or gross diminution of pulsation in the arteries of the foot after exercise (inverse reaction)
(3) The absence of both posterior tibial pulses

On these criteria Semple found that of 100 diabetics over the age of 50 42 had signs of arterial disease Intermittent claudication was however a rare symptom and in only 6 cases was the popliteal pulse absent On the other hand the incidence of gangrene of the extremities was high and it appears that in diabetics it is mainly the smaller muscular arteries which are involved It has frequently been stressed by clinicians that gangrene in diabetics is often due to thrombosis of digital vessels (Lewis 1946 Learmonth 1950) while Warren (1930) brought forward evidence based on his pathological studies to show that the arterial lesion

in diabetes is distal in so far as it chiefly involves the smaller muscular arteries the larger vessels often remaining intact Finally the occurrence of peripheral arterial disease in diabetes is more closely related to the age of the patient than to the duration of the diabetes and Oakley (1955) has stressed that it is only excessively common in diabetics over the age of 60

For lesions of the feet see also Chapter XII

3 **Diabetic Retinopathy** Retinal changes were first noted in diabetes by Jaeger (1856) and Hirschberg (1890) described a characteristic inflammation of the central region of the retina with small bright spots and scattered haemorrhagic points This change he termed *retinitis centralis punctata diabetica* and is a descriptive term for what is still recognized as the characteristic appearance of early diabetic retinopathy

The increasing frequency with which retinal changes are now being observed appears to be directly related to the increasing longevity of the diabetic patient Thus Wagener and Wilder (1921) found diabetic retinopathy in 8 3 per cent of their cases while Wagener Dry and Wilder (1934) found that the incidence had risen to 17 7 per cent and Wagener (1945) reported that 29 6 per cent of his diabetic patients had retinal changes

The pathological change in the retina has been investigated by Ballantyne and Loewenstein (1943 1944) Ballantyne (1945) and Ashton (1949) These workers have concluded that diabetic retinopathy is quite distinct from the retinopathy of hypertension This is supported by the clinical observations of others (Croom and Scott 1949) that *retinal sclerosis* is not marked in diabetics and that in 9 of their cases with retinopathy the retinal arteries were normal By studies on specially stained sections Ballantyne and Loewenstein concluded that the punctate haemorrhages seen on ophthalmoscopy are globular micro aneurysms associated with the capillaries in the inner nuclear layer of the retina They also showed that the micro-aneurysms were usually related to the venous side of the capillary network

Clinically it is now accepted that the duration of the

disease is the most important factor in the development of diabetic retinopathy the age of the patient and the severity of the diabetes being of less importance On the other hand although retinopathy is sometimes seen in mild cases it is believed by many that good diabetic control is the best prophylaxis against the development of this complication All diabetics should have regular ophthalmoscopic examinations The earliest changes are the presence of the micro aneurysms already described They appear as pin point globular petechial spots often in the region of the macula and usually clustered around a vein More extensive haemorrhages may later take place from the micro aneurysms and exudates often develop in association with them The exudates are often punctate (*retinitis punctata*) but may coalesce and form large masses of hard exudate

In cases of longstanding diabetic retinopathy and especially in those with hypertension it is not uncommon for gross retinal haemorrhages or for vitreous haemorrhages to occur Rapidly developing blindness may result from such haemorrhages and they also carry the risk of secondary glaucoma Retinal and vitreous haemorrhages are also frequently followed by the formation of new blood vessels (*retinitis proliferans*) which tend to be tortuous and protrude forward from the surface of the retina in such a way as to cause gross impairment of vision

The prognosis as far as sight is concerned in the uncomplicated case of diabetic retinopathy is rather less gloomy though the danger of a sudden haemorrhage is always present On the other hand the condition often remains unchanged with no signs of progression over a number of years

No specific remedy has been proved of value Rutin has been tried without convincing results and prophylaxis by good diabetic control remains the best method of prevention at present See also Chapter X

4 Hypertension in Diabetes The blood pressure in diabetes has been studied by many workers and there is no doubt that hypertension is more common in diabetic than in non diabetic persons Major (19 9) in a statistical study showed that at comparably advanced ages the frequency of a

systolic blood pressure above 150 mm Hg was higher in diabetics than in non diabetics Bell and Clawson (1938) found that hypertension was 2 3 times as frequent in the elderly diabetic as in non diabetics of the same age group but they observed that only 5 5 per cent of hypertensive patients become diabetic Friedman (1935) reported hypertension in 56 per cent of his diabetic patients Root and Sharkey (1936A) reported 54 per cent and Edeiken (1945) reported a 38 per cent incidence

Hypertension in diabetics is more common in women especially those who are overweight than in men and the high incidence in diabetics becomes more noticeable in patients over the age of 40 The reasons for the high incidence of hypertension in diabetics are not fully understood In a number of cases the hypertension is clearly of renal origin as in those cases with evidence of chronic pyelonephritis or signs to suggest the presence of diabetic nephropathy On the other hand only a small proportion of hypertensive diabetics have any evidence of renal damage and many of the features of the hypertension suggest that it is of the benign essential type Indeed Balme and Cole (1951) have shown that when hypertension occurs in diabetics over the age of 40 it resembles essential hypertension in its heredity age and sex incidence Thus the incidence of a hypertensive family history is greater amongst hypertensive diabetics than among diabetics with a normal blood pressure it is commoner among obese women than among the men and the incidence of hypertension tends to rise with the age of the patient Furthermore the essentially benign nature of the hypertension in the majority of cases is borne out by the long period of time over which many diabetic patients are found to be hypertensive without suffering any severe hypertensive symptoms On the other hand Root and Sharkey (1936B) have found on autopsy studies that although hypertensive changes were rarely prominent in the heart muscle of diabetics known to have hypertension in life yet coronary artery occlusion was four times as common when hypertension was present as when it was not This perhaps emphasizes the fact that although hypertension and atheroma are often

met with in the same patient they are not necessarily parallel conditions

Certainly in clinical practice although hypertension is frequently found in diabetics active hypotensive therapy is only rarely required

MALIGNANT VASCULAR DISEASE

It has been suggested that adrenocortical hyperfunction may be a factor in the causation of vascular damage in diabetes and comparison has been drawn between the vascular changes in Cushing s syndrome and those that may be produced in diabetic animals by cortical administration (Kinsell *et al* 1954) Furthermore Poulsen (1953) observed a definite regression of the diabetic retinopathy in a patient who developed post partum necrosis of the anterior pituitary gland Adrenalectomy and hypophysectomy have both been performed in cases of advanced diabetic vascular disease in the hope that its progress might be arrested

Wortham and Headstream (1954) carried out bilateral total adrenalectomy in seven diabetic patients with severe degenerative vascular disease The ages of the patients varied from 23 to 54 years and in all but two the duration of diabetes from the time of diagnosis was more than 13 years Nearly all gave a history of poor diabetic control and all had evidence of extensive vascular disease as manifested by hypertension albuminuria oedema and retinal change Post operatively the patients were maintained on cortisone and hydrocortisone without other adrenal steroids In four cases there was either arrest or improvement in the retinal changes and also a slight fall in blood pressure The degree of albuminuria and oedema was reduced in three cases and in five patients there was a post-operative fall in insulin requirement in spite of the diabetogenic nature of the cortisone on which they were being maintained At the time of the report three patients had died—one from adrenal insufficiency one from a cerebrovascular accident and another from a cardiac infarct

Malins (1956) reported the results of adrenalectomy in 6 diabetics One already uraemic died of renal failure two

weeks after the operation Retinopathy was improved in 1 unchanged in 3 and worse in 1 Albuminuria was unchanged in the 2 patients in whom it was found before the operation and the control of the diabetes was unchanged The general health was better in 1 patient an unchanged in 4

Luft *et al* (1955) reviewed the results of hypophysectomy performed on 20 diabetic patients aged between 20 and 33 years Death occurred in 7 cases Substitution therapy included the administration of thyroxine oestrogens or androgens and adrenocortical hormone or D C A In the surviving cases there was a fall in blood pressure and a decrease in heart volume A definite decrease in albuminuria and in glomerular filtration was achieved but the effective renal plasma flow remained unchanged No signs of progression of the renal disease were observed the visual capacity improved in some cases and the retinal changes did not progress further

It would however seem unlikely that such radical measures are likely to have a permanent place in the treatment of these tragic complications of diabetes and every effort must clearly be directed towards determining more exactly their pathogenesis so that they may be prevented from developing

At present good diabetic control appears to be the best prophylactic measure

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CHAPTER X

THE DIABETIC EYE

BECAUSE the changes in diabetic retinopathy are almost specific it is not surprising that diabetic retinopathy is regarded as the classical ocular complication of diabetes On the other hand there is a high incidence of cataract amongst diabetics and a number of other ocular conditions are not uncommonly seen This was well illustrated in a personal series of 100 diabetic patients referred by ophthalmologists 84 of the cases were seen at Moorfields Eye Hospital and 16 at general hospitals There were 34 male and 66 female cases with ages varying from 11 to 87 years their ages being summarized in Table 1 66 of the patients were newly diagnosed diabetics in whom the presenting symptoms were ocular and the remaining 34 patients were known diabetics developing an ophthalmic lesion

Table 1 AGE DISTRIBUTION OF 100 DIABETIC PATIENTS REFERRED BY OPHTHALMOLOGISTS

Under 30	4
31–40	5
41–50	10
51–60	23
61–70	31
71–80	21
81 +	6
	100

The wide range of ocular conditions which may occur in diabetics is shown in Table 2

A few of the associations are obviously no more than coincidental the two conditions being aetiologically unrelated The case of retinoblastoma and the one of intra-ocular foreign body in both of whom glycosuria was discovered in routine urinalysis are examples of this—but in the majority

of other cases the ophthalmic lesions could well be related to the diabetic state

Table 2 Ocular Conditions Occurring in 100 Diabetics

	No Cases		
	New Cases (66)	Known Diabetics (34)	Total
Cataract	22	13	35
Retinopathy	19	12	31
Retinopathy + Cataract	7		7
Retinopathy + Iritis	3	1	4
Blurring of vision	3		3
Iritis	2	1	3
Glaucoma	2	2	4
Cranial Nerve Palsy	2	2	4
Retinal Detachment	1	1	2
Optic Atrophy		1	1
Central Scotoma		1	1
Homonymous Hemianopia	1		1
Intraocular haemorrhage	1		1
Blepharitis	1		1
Retinoblastoma	1		1
Intraocular Foreign Body	1		1

Diabetic Retinopathy

The vascular changes in the retina which are classical of this condition have already been described (Chap IX) Ophthalmoscopically the earliest lesion—the micro aneurysm can be identified as a pin head haemorrhagic spot or as a cluster of such lesions usually in the region of the macula and in juxtaposition to the veins of the choroidal capillary network (Fig X 1) In more advanced cases there are exudates (Figs X 2 and 3)

It is generally believed that diabetic retinopathy does not usually develop until the disease has been present for upwards of ten years This is certainly the case on clinical experience with young diabetics in whom the date of onset of diabetes may be reasonably accurately ascertained Thus Hardin *et al* (1956) found that in 140 juvenile diabetics observed over

periods of 10–29 years the average time required for the development of diabetic retinopathy was 13 years. With older diabetics the date of onset is more difficult to determine and it is often assumed that a mild diabetic state may have existed for many years before the condition is finally diagnosed. This could well explain the finding of Nabarro (1957)



(By courtesy of [illegible])

FIG. X 1. Retinal vessels injected with Indian ink to demonstrate micro aneurysm

that older diabetics are often found to have diabetic retinopathy within a few years of the onset and the observations that it may be a presenting feature of the disease in many middle aged diabetics. It is also believed that bad diabetic control predisposes to its development (Keiding, Root and Marble 1952). This was well illustrated in the 12 known cases of diabetes referred for restabilization when they developed diabetic retinopathy (personal series *vide supra*). The average age of the cases was 55 years with an age range 31–69 years and an average duration since diagnosis of 10·3

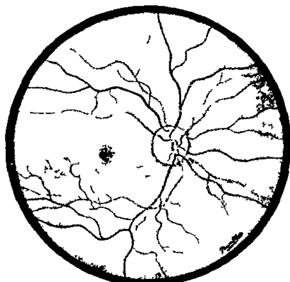


Fig. [illegible].—Early diabetic retinopathy

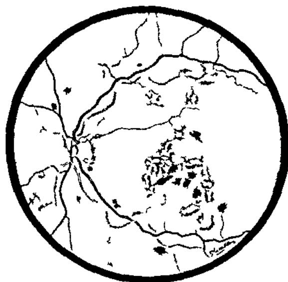


Fig. 3.—Advanced diabetic retinopathy

years Several admitted that they had had no supervision of their diabetes for years one stated that having been caught in an air raid on her way to the diabetic clinic she never attended again On the other hand although there seems good evidence that retinopathy does not develop until the disease has been present for about 10 years there is also evidence to show that it may occur in relatively mild cases Thus in 30 patients shown in Table 2 the diagnosis was only made when the retinopathy caused failing vision It seems reasonable to assume that these patients had been diabetic for upwards of 10 years and on questioning a number admitted mild symptoms which would confirm this yet their diabetic state can never have been severe enough to cause any dangerous degree of ketosis and in several cases the diabetes came under control with diet alone or with diet and a small dose of insulin Thus although there may be a greater chance of developing retinopathy in uncontrolled diabetes the actual severity of the diabetic state seems to bear less relation to its development than the duration of the disease Unfortunately there is no simple treatment which has been found effective in reversing the changes of diabetic retinopathy and although Poulsen (1953) observed a regression after a patient developed Addison s disease there seems little likelihood that adrenalectomy or hypophysectomy will become established methods of treating the condition Rutin has been of little value and at present the early diagnosis of diabetes and the maintenance of reasonable control seem to be the best methods of preventing the development of this tragic diabetic complication

Cataract

It still seems a matter of doubt whether or not cataract is more common in diabetic than in non diabetic persons O Brien Molsberry and Allen (1934) studied the well recognized acute cataract of young diabetics They pointed out that although it was usually considered rare and characteristically develops rapidly and bilaterally they found such changes in 20 (16 per cent) of 126 cases Waite and Beetham (1935) thought that apart from these acute cataracts the incidence of cataracts in diabetics was no higher than in non

diabetics although a thorough investigation by Anthonisen (1936) did not support their findings He examined the incidence of diabetes in a series of patients admitted to hospital for cataract operations and found that the condition was statistically much more common in diabetics than in non diabetics He was careful to emphasize that he was only considering cases of cataract severe enough to require operation and thought that it was the inclusion of even the most minor degrees of lens opacities in comparative series that made cataract appear as common a finding in non diabetics as in diabetics

That glycosuria can in fact cause cataracts has been conclusively shown by Foglia and Cramer (1944) who found that in rats with 5 per cent pancreas remaining after pancreatectomy cataracts appeared after a period of time from 50 days onward Nevertheless Joslin (1952) considers that until more careful study is made of cases operated on for cataract in large ophthalmological centres it will be impossible to settle the primary question as to whether diabetes does actually produce more cases of cataract than are found in non diabetics

In a personal series 42 of the 100 cases referred by ophthalmologists had cataracts 29 new cases of diabetes being discovered when the patients sought treatment of their cataracts and the remaining 13 cases being known diabetics who were referred for restabilization prior to cataract extraction Only one of these cases had true diabetic cataracts He was a lad of 18 who had been a severe diabetic for four years badly controlled and attending no clinic He developed classical bilateral diabetic cataracts over a period of 3–6 months As already noted this condition is well recognized as occurring in young severe diabetics and is usually regarded as rare but fortunately responds fairly well to treatment (Fig X 4)

The association of diabetes with senile cataract still requires further elucidation and a good statistical survey of the true incidence of senile cataract in diabetics compared with the general population still seems lacking and is a project worthy of study

From clinical experience it seems that even though senile

cataract may not be much more common in diabetics than in non diabetics their development is accelerated by the diabetic state and from the practical point of view many new cases of diabetes are discovered in ophthalmic departments when they present with failing vision due to cataracts From this it would appear that the general practitioner is not sufficiently aware of the association between cataract and diabetes mellitus and it is suggested that routine test for glycosuria should be carried out before cases of cataract are referred to the ophthalmologist A significant amount of time

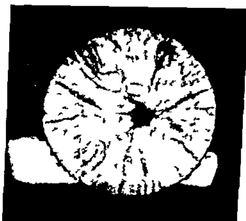


FIG X 4 —Diabetic Cataract showing dense flocculent opacity

could be saved in ophthalmic out patient departments if this routine were established and any case in which glycosuria was discovered should then be referred to the physician for investigation and stabilization before being sent to the ophthalmologist for treatment of the cataract

Changes in Refraction Blurring of vision is a common symptom in recently diagnosed diabetics and in those undergoing stabilization when there may be wide variations in the sugar content of the refractile media In certain cases (Table 2) it may actually be the symptom which leads to diagnosis

Duke Elder (1949) has suggested that the essential features are that a myopic change is associated with a rise and a

hypermetropic change with a fall in the blood sugar level He thought that myopia associated with a rising sugar concentration was due to hydration of the cortical layers of the lens relative to the nucleus As the blood sugar rises the osmotic pressure of the aqueous tends to decrease owing to the great elimination of electrolytes that occurs with the polyuria of uncontrolled diabetics and to establish osmotic equilibrium fluid flows from the chambers of the eye into the lens If the inflow of fluid is rapid actual droplets are formed under the capsule of such a size that they can be seen with the slit lamp and eventually an acute diabetic cataract may develop—sometimes with great rapidity When the blood sugar falls the lens may shrink and hypermetropia results Other views have been expressed regarding the exact cause of the changes in refraction which occur in uncontrolled diabetes and Weekers (1941) thought that myopia was due to an increased refractive index of the lens due to changes of a pre cataract nature caused by a toxic agent Such changes he regards as reversible and on their amelioration hypermetropia results

In any event it is important to recognize that alterations in the refractile media may cause blurring of vision and that this may be the presenting symptom of diabetes and secondly it is important to warn patients undergoing stabilization that until they have become stable they may suffer from blurring of vision owing to the fluctuation in blood sugar level causing alterations in the shape of the lens

Ocular Nerve Palsies

Ocular nerve palsies are said to be more common in diabetics than in non diabetics (Waite J H Beetham W P 1935) Dieulafoy (1905) reviewed the literature and found 59 cases reported at that time Leopold (1945) noted a 5 per cent incidence of ocular nerve palsy in a series of 100 cases of diabetes studied for 10 years or more The oculomotor nerve is most commonly affected but paresis of the IVth and VIth nerves may also occur Several workers have stressed that the prognosis is good and that the paresis tends to recover in 2–3 months (Waind 1956 Brain 1955) On the other

hand there is a tendency for the paresis to recur (Dieulafoy 1905 McAlpine 1956) (There is little agreement on the aetiology of cranial nerve lesions in diabetics and although it has sometimes been suggested that they may occur as a manifestation of diabetic neuropathy (Root 1933) it would seem probable that a vascular lesions such as an intramedullary thrombosis or haemorrhage is more often the cause (Weinstein and Dolger 1948))

The association of ocular nerve palsies with severe head ache has recently been stressed (Harris Jones 1956 Jackson 1955 Waind 1956) It has previously been considered that the pain was due to orbital periostitis affecting the spheroidal fissure but the possibility of an accompanying trigeminal neuralgia has been suggested by Martin (1953) and Goodman *et al* (1953) From the practical point of view however it is sufficient to recognize that ocular nerve palsies are not uncommon in diabetics and that the prognosis is generally good although there is a certain tendency for the paresis to recur

OTHER OCULAR LESIONS

The vascular lesions which may occur include vitreous haemorrhages and cerebral thromboses causing homonymous hemaniopa The more unusual neurological manifestations include iridoplegia (non syphilitic Argyll Robertson pupils) retrobulbar neuritis and optic atrophy In the case of optic atrophy it should be said that although the condition is reported as occurring in diabetics (Paley and Tunbridge 1956) some of the cases reported seem to be more likely to have been cases of familial optic atrophy Similarly it is difficult to be certain as to whether there is any causal relationship between retrobulbar neuritis and diabetes although in a personal case there was an improvement in the retrobulbar neuritis after the patient s diabetic state was brought under good control but this too could well have been coincidence

Inflammatory lesions of all kinds are common in diabetics and the occurrence of iritis and certainly of blepharitis may well be an expression of this Finally although there is no

suggestion that glaucoma is commoner in diabetics than in non diabetics the association between the two conditions may be important In four personal cases the patients have developed severe ketosis which had been precipitated by vomiting due to acute glaucoma In two cases this was the mode of presentation of diabetes while the other two cases became unstable when they developed glaucoma

In concluding this chapter it should again be emphasized that diabetic retinopathy is certainly the most classical complication of diabetes but other conditions may occur and in particular senile cataract is a common association Diabetic retinopathy seems to be related to the duration of the diabetes but although its development may be accelerated by poor control it can also occur in relatively mild cases Senile cataract is a not infrequent mode of presentation of diabetes and any patient with cataract should have a urine examination for sugar before being sent to an ophthalmologist

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CHAPTER XI

THE DIABETIC KIDNEY AND URINARY TRACT

THERE are a considerable number of lesions affecting the kidney and the renal tract which occur in diabetics As already noted the most characteristic lesion is intercapillary *glomerulosclerosis which is now regarded* as an almost specific diabetic lesion associated with a clinical syndrome of diabetes with albuminuria and generalized oedema and is now known as diabetic nephropathy In addition to this lesion the diabetic appears to be peculiarly liable to urinary tract infection and recurrent attacks of pyelitis may occasionally be complicated by pyelonephritis or papillary necrosis Tubular lesions such as salt losing nephritis may further complicate attacks of pyelitis in the diabetic A convenient classification of renal lesions in diabetics has been suggested by Smith Bolton and Turnbull (1955) as a result of an extensive histological study

Further consideration of renal lesions in diabetics will be confined to those which commonly occur in clinical practice and they will be discussed under the headings of diabetic *nephropathy and infections of the kidney and the renal* tract (Table 1 p 155)

I DIABETIC NEPHROPATHY

A lesion of the renal glomeruli associated clinically with diabetes albuminuria hypertension and oedema of the nephrotic type was described by Kimmelstiel and Wilson in 1936 During a pathological study of renal disease these workers discovered eight cases in which there was a striking hyaline thickening of the intercapillary connective tissue which they termed intercapillary glomerulosclerosis In all but one of the cases there was a history of diabetes and in several of the cases the nephrotic syndrome had been present with oedema and heavy albuminuria These glomerular changes have since been noted by many other workers and

in the fully developed Kimmelstiel Wilson syndrome * the triad of albuminuria hypertension and retinopathy is nearly always present Indeed the frequent coincidence of diabetic retinopathy with evidence of renal disease has long been recognized Thus Onfray (1919) found that diabetic retino-



(By courtesy of Norman Ashton)

Fig XI 1 —Intercapillary glomerulosclerosis

pathy was often associated with hypertension and nephritis and Garrod (1920) made a similar observation Furthermore although the micro aneurysm has not been convincingly demonstrated in any organ other than the retina the suggestion has been made by Ashton (1949) that intercapillary glomerulosclerosis and retinopathy may be manifestations of the same pathological process modified by the different anatomical structure of the retinal and renal vessels

Although the histological picture described by Kimmelstiel and Wilson is usually present in the kidneys of diabetic

* This is strictly a pathological syndrome

patients dying with signs of renal insufficiency it is probable that other factors frequently contribute to what may be called diabetic nephropathy Wilson Root and Marble (1953) have suggested that a mixed aetology is usually present and that histopathological findings characteristic of diabetic nephropathy consist of a combination of lesions including all or most of the following acute and chronic pyelonephritis arteriosclerosis and intercapillary glomerulosclerosis See Fig XI 1

Prevention of this serious complication depends upon good diabetic control and the prevention or energetic treatment of urinary infections in diabetics

The onset of diabetic nephropathy is insidious and is rare before the disease has been established for 12 15 years The first sign is of intermittent proteinuria which becomes apparent on routine urine tests at clinic attendance Ophthalmoscopic examination may at this stage reveal the presence of occasional micro aneurysms Proteinuria perhaps over the next two or three years gradually becomes constant peripheral oedema becomes marked hypertensive levels are found when blood pressure readings are taken and the blood urea value is found to be slightly increased By this stage typical diabetic retinopathy with haemorrhages soft and hard exudates and early areas of retinitis proliferans is established Once this stage has been reached the degree of renal insufficiency continues to progress—with the development of massive proteinuria which results in hypoproteinaemia anaemia and constant azotemia Although there may be fluctuations in the clinical course it is relentlessly progressive and the terminal months are marked by persistent hypertension uraemia cardiac failure and often blindness Death is usually due to uraemia cardiac failure or myocardial infarction As the renal insufficiency becomes more severe it is frequently found that the diabetes seems to ameliorate and the insulin requirement falls

Dana *et al* (1951) suggested that a specific type of diabetes characterized by such amelioration of the severity of the disease and by the infrequent occurrence of acidosis is associated with the Kimmelstiel Wilson lesion *per se*

Runyan Hurwitz and Robbins (1955) have been unable to find any evidence to support this suggestion They found that both amelioration and increased severity of diabetes as judged by changes in insulin dosage occurred in patients without relation to the pathological lesions On the other hand amelioration of the diabetes was often observed in patients with oedema albuminuria and hypertension and they suggest that a decrease in food intake in patients with this syndrome may contribute greatly to such an amelioration It is doubtful however whether this is the full explanation and it should be particularly remembered that the original description of intercapillary glomerulosclerosis by Kimmelstiel and Wilson was purely pathological and that confusion can arise when histological findings are translated into a clinical syndrome without qualification

The most alarming aspect of diabetic nephropathy comes from the observation of Wilson Root and Marble (1951) that it occurs most frequently among patients in their thirties and forties who have had severe poorly controlled diabetes for 20 years or more Thus 62 patients (25 per cent) among a group of 247 young patients with severe diabetes of more than 10 years duration had manifestations of diabetic nephropathy On the other hand among the 247 patients there were 37 who had maintained excellent or good diabetic control (by exacting standards) and who had submitted themselves for regular medical examination and daily urine tests with adjustment of diet and insulin to secure sugar free specimens Not one of these had developed nephropathy at the time of the report Nevertheless it is doubtful whether diabetic control in itself is enough to prevent the development of diabetic vascular disease

II INFECTIONS OF THE KIDNEY AND THE *RENAL TRACT*

1 **Urinary Tract Infection** Infection of the urinary tract is common in diabetics especially in diabetic women and it is more common in cases of uncontrolled or inadequately controlled diabetes (Sharkey and Root 1935)

It often causes no dramatic symptoms remaining as a chronic condition and sometimes only being diagnosed when

the discovery of albuminuria prompts the examination and culture of a catheter specimen of urine Infections of the lower urinary tract in diabetics tend to be intractable The persistence of the infection is probably related to a combination of factors including poor diabetic control with persistent glycosuria faulty hygiene and sometimes repeated catheterization (Sharkey and Root 1935) Obstructive lesions in the urinary tract may sometimes be the cause of failure to eradicate the infection and Rhoads (1952) stresses the importance of carrying out full genito-urinary investigations to exclude an obstructive lesion whenever there is evidence to suggest one The responsible organisms are nearly always colon dwelling bacteria and this is consistent with the belief that infections of the urinary tract in diabetics are usually ascending infections the portal of entry being by the urethra rather than by the blood stream (Barnard *et al* 1953)

Management of Urinary Infections Because of the dangers of the patient developing pyelonephritis and other renal complications it is essential to attempt to eradicate infection in the urinary tract The clinician must be aware of the habit of the diabetic to develop renal complications and a routine test for albumen should be performed in addition to tests for glycosuria at every clinic attendance The discovery of albuminuria may indicate the presence of nephropathy but any patient not previously known to have this diabetic complication and who is found to have albuminuria on two or more consecutive clinic attendances should have a laboratory examination of a mid stream specimen in the case of a male or a catheter specimen of urine in the case of a female If culture of the urine yields a bacterial growth it is then essential that sensitivity tests to the current range of antibiotic drugs should be carried out and a full course of the appropriate antibiotic must be given Should there be specific symptoms of infection it is justifiable to initiate a course of chloramphenicol (0 25 G q i d for 5 days) or nitrofurantoin (Furadantin) (average adult dose 100 mg q i d with meals) whilst awaiting the results of the sensitivity tests On completion of the course a few days should be allowed to elapse and a further catheter specimen of

urine should then be examined Should the infection still be present the sensitivity should be re determined and a further course of antibiotic prescribed

Inadequate treatment may sometimes be the cause of the chronicity of these infections and it is essential to be persistent in attempting to eradicate them

It is only in those cases where there is a suggestive symptom such as renal colic unilateral pain haematuria or persistent symptoms of cystitis that it is justifiable to proceed to intravenous pyelography cystoscopy and retrograde examination and indeed there is much to be said against instrumentation in most cases although Rhoads (1952) has stated that he has commonly found obstructive lesions on routine genito urinary investigation in these cases It would not seem practicable to carry out full investigation on the majority of the cases seen in practice in the absence of symptoms such as those mentioned above Finally in attempting to prevent the recurrence of urinary infections it is important for the patient to understand the necessity of strict perineal hygiene and also of maintaining the best diabetic control possible

2 Pyelonephritis Although it may be seen from Table 1 that pyaemic abscesses and renal tuberculosis may occur in diabetics pyelonephritis is the renal complication which may be of the greatest practical importance This may be an acute fulminating condition liable to be associated with renal papillary necrosis or it may be a chronic condition which is only recognised at autopsy The incidence of papillary necrosis from autopsy studies on diabetics has been reported as 3 37 per cent (Edmondson *et al* 1947) approximately 4 5 per cent (Robbins *et al* 1946) while Smith *et al* (1955) found 6 cases in their series of 219 autopsies Edmondson (1947) and Robbins *et al* (1946) both found this change in approximately 25 per cent of their cases with pyelonephritis

The persistence of pyuria with rigors hypertension and signs of impaired renal function must suggest the presence of pyelonephritis On the other hand Joron (1955) found the recognition of acute pyelonephritis often difficult in the diabetic and of 23 cases only 3 had pain in the loin and only 2

had renal tenderness As a group the patients were much more ill than could be explained by physical findings although pus was not always found in the urine He stressed the importance of repeated examination of catheter specimens of urine

Table 1 FREQUENCY OF DIFFERENT RENAL LESIONS FOUND IN 219 DIABETIC PATIENTS WHOSE KIDNEYS WERE EXAMINED HISTOLOGICALLY

After Smith J F *et al* J Path Bact (1955) LXX 478

Total no of subjects studied	Males		Females	
1 Intercapillary glomerulosclerosis	11		107	
2 Infections of the kidney	)		23	
Acute pyelonephritis				
(a) without medullary necrosis	1	10	2	10
(b) with medullary necrosis	3		3	
Pyaemic abscesses	3		3	
Chronic pyelonephritis (all slight and focal)	2		2	
Tuberculosis	1		0	
3 Other renal lesions				
Acute nephritis	0	7	1	7
Chronic nephritis	3		0	
Benign and malignant nephrosclerosis	1		5	
Symmetrical cortical necrosis	1		0	
Lower nephron nephrosis	0		1	
Thrombosis of renal veins	1		0	
Carcinoma	1		0	

Garrett *et al* (1954) have stated that renal papillary necrosis must be suspected in any diabetic with severe acute pyelonephritis gross haematuria renal colic micturition of solid material or rapidly progressive renal insufficiency not responsive to chemotherapy and diabetic management They have found that this condition may be an acute fulminating and rapidly fatal process or may be relatively chronic and progressive with or without intermittent or terminal acute fulminating episodes

*In the management of these cases the treatment of the in*fection is the urgent problem (*vide supra*) Surgical intervention to relieve an obstruction may be necessary and in certain cases nephrectomy *may be life saving Alternatively it has* occasionally been found beneficial to irrigate the pelvis and ureter with streptokinase streptodornase to produce lysis of the slough

Chronic pyelonephritis may develop as the result of long standing urinary tract infection and may be partly responsible for the progressive renal impairment and hypertension so commonly seen in the female diabetics (Bowen and Kutzman 1942) On the other hand Smith *et al* (1955) commented on their finding that chronic pyelonephritis was a *relatively uncommon autopsy finding and was not respons*ible for renal failure in any patient

Although it is rare it should be noted that pyelonephritis may occasionally be complicated by *salt losing nephritis* due to tubular changes The condition first described by Thorn *et al* (1944) gives rise to a clinical picture akin to that of Addison s disease with crises When this occurs in the diabetic with pyelonephritis the diagnosis and the management of the case present the greatest difficulties

Initially the patient may be thought to be developing diabetic pre coma but *the hypotension fails to recover with* hydration and insulin and the patient continues to excrete sodium and chloride in the urine At the same time the insulin requirement *remains high contrary to* what would be expected were the collapse due to adreno-cortical insufficiency It is only when the condition is recognized as being due to salt losing nephritis complicating pyelonephritis and the electrolyte balance restored that the patient may recover At the same time it is vital to treat the infection energetically and although the ultimate prognosis is poor it may be possible to overcome the immediate crisis

III Other Lesions

Conditions which occur in the non diabetic may likewise occur in diabetics and must be considered in the differential

diagnosis of any complication affecting the kidney or the renal tract

Ischaemic lesions may occur in diabetic kidneys in the absence of intercapillary glomerulosclerosis. In their series Smith *et al* (1955) found 6 such cases 5 of whom they considered to have malignant hypertension and 4 had suffered from moderate hypertension with severe vascular degeneration and heart failure. These cases they classified as having decompensated benign nephrosclerosis

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CHAPTER XII

DIABETIC FEET

In the past it has been customary to describe any necrotic lesion on the feet of diabetics as diabetic gangrene There are however several factors involved in the development of such lesions and it is important to recognize the aetiology of the lesion in each case as this may materially alter treatment Oakley (1955) has classified the lesions on the feet of diabetics into four groups

(1) Septic lesions
(2) Ischaemic lesions
(3) Neuropathic lesions
(4) Mixed lesions

1 **Septic lesions** A diabetic is more susceptible to sepsis than a non diabetic and septic lesions may occur on the feet On the other hand a lesion on the foot of diabetics is rarely primarily septic and careful examination will usually reveal evidence of vascular insufficiency or neuropathy

2 **Ischaemic lesions** The high incidence of peripheral vascular disease in diabetics has already been stressed and it has been pointed out that it is more closely related to the age of the patient than to the duration of the disease or to the adequacy of diabetic control (Oakley 1955) Ischaemic lesions are therefore most commonly met in patients over the age of 60 Occasionally a younger patient may develop ischaemic lesions and these are usually due to digital vessel thrombosis as occurred in the case illustrated in Figs XII 1 and 2 In this patient an intelligent male aged 38 the lesions on the feet were the presenting features of diabetes although on questioning he admitted having frank diabetic symptoms of thirst and polyuria and on examination he had signs of neuropathy with absent knee and ankle jerks It was then possible to identify the lesion on the dorsum of the foot as being due to hot water bottle burns so that the lesions on the feet had a mixed aetiology being neuro-

vascular in type Local amputation of the right middle toe was the only surgical intervention required the digital artery being completely occluded All the remaining lesions healed when diabetic control was established and the knee and ankle jerks have subsequently returned



FIG XII 1 —N u ascular changes n the f et f a d betic

In the more characteristic ischaemic foot an area of gan grene develops in the toe or on one of the pressure points of the foot such as the heel or the medial or lateral borders of the foot Pulsation is usually absent from the dorsalis pedes and posterior tibial arteries and the foot is cold In severe cases the tendency is for the lesion to spread proximally from



FIG XII 2—Neurovascular changes in the feet of a diabetic



FIG XII 3—Trophic ulcer over metatarsal heads

the toe to the dorsum of the foot Pain is often a prominent feature when the nervous system is intact and it may be so severe that urgent amputation is required The painful ischaemic foot is characteristically pink in addition to being





Fig XII 4 —Charcot joint Diabetic neuropathy

cold There is almost never any alternative to some form of amputation in ischaemic diabetic gangrene and details of treatment will be discussed later

3 Neuropathic Lesions The full importance of neuropathic lesions in the feet of diabetics has only recently been recognized The earliest change is a thickening and scaling

of the skin of the sole of the foot with a tendency to callous corn and bunion formation. At the same time there frequently develops a clawing deformity of the small toes. Continued pressure and repeated trauma on an imperfectly innervated foot, especially in the presence of ill fitting foot wear, leads to the development of perforating ulcers which have long been recognized as a *manifestation of neuropathy*. They occur most commonly over the metatarsal heads and are most resistant to treatment (Fig. XII 3). Finally certain characteristic changes in the joints of the tarsus may occur in diabetic neuropathy. Although bony lesions in the feet of diabetics have long been recognized, they have often previously been regarded as evidence of osteomyelitis, especially as sequestration is not uncommon, but it is now generally accepted that they are much more frequently neuropathic in nature (see Chapter XIII). Bailey and Root (1947) described *the painless destruction of the tarsus in seventeen patients* with poorly controlled diabetes and numerous other workers have since noted similar changes in diabetics with signs of neuropathy (Fig. XII 4). The tarsus may eventually become completely disorganized and the foot may become so swollen and deformed that amputation is the only possible treatment. Neuropathic changes have also been noted in the larger joints such as the knee (Morris 1947, Wilson *et al.* 1949, Shore 1947, Spear 1947, Parsons and Norton 1951). Similarly the changes may be localized in the hallux when *the earliest sign is often a shortening and broadening* of this digit.

4 **Mixed Lesions.** In many diabetics, especially those in the older age groups, both the blood supply and the nerve supply to the periphery are inadequate. These patients are particularly liable to develop lesions on their feet and in these cases the aetiology must clearly be described as neurovascular and sepsis is often an added complicating factor.

Management

The management of each diabetic who develops a lesion on the foot has to be determined on its own merits. Ideally the majority of cases should be hospitalized and in the first

instance it is important to assess the type of the lesion and thereafter certain principles for the management of each type of case must be followed

Septic Lesions Some degree of sepsis complicates the majority of lesions even if it is not the primary factor and every effort must be made to eradicate the infection This requires the isolation of any organism obtained from swabs and the determination of the effective antibiotic by sensitivity tests Parenteral therapy is often of limited value when the blood supply is poor and the appropriate antibiotic must be applied locally At the same time it is important to establish adequate drainage and the separation of sloughs is often assisted by Eusol dressings Vaseline gauze is usually an unsatisfactory dressing as it tends to keep the lesion boggy and indeed it is well to expose the lesions to the air as much as possible

Ischaemic Lesions The ischaemic foot should be kept cool It is extremely difficult to improve the blood supply in the diabetic with extensive peripheral vascular disease Vasodilator drugs such as Priscol and Ronicol give disappointing results Buerger s exercises are again of little value Anticoagulant therapy is sometimes given a trial on the assumption that repeated thrombotic episodes may be a contributory factor in ischaemic gangrene This is often worth while because even although the blood supply may show little improvement there may be a dramatic relief of pain with anticoagulant therapy and this seems particularly to be related to injections of heparin Sympathectomy has few advocates although Cohen (1955) believes it should be tried more often He has claimed that after sympathectomy the foot blood supply can be doubled and the foot remains warm and withstands minor trauma much better He also claims that sympathectomy often relieves ischaemic resting pain quite dramatically and the improved blood supply may facilitate better healing if amputation eventually becomes necessary On the other hand he considers there are definite contraindications to sympathectomy These include cases with extensive sepsis and cases with cold cyanotic feet as this indicates poor circulation flow and capillary paresis

and the release of arteriolar tone after sympathectomy increases the capillary stasis and the gangrene tends to spread He also considers that gangrenous areas should be allowed to localize as well as possible before sympathectomy and that patients with diffuse generalized arteriosclerosis are not considered good subjects Unfortunately this is so often the case that most workers have found the results of sympathectomy most disappointing and have found that the only real benefit conferred by the operation is the relief of ischaemic pain Indeed as already pointed out there is almost never any alternative to some form of amputation in ischaemic diabetic gangrene although the more conservative measures indicated above are always worthy of a trial and when amputation does become obligatory it is wise to be as conservative as possible in the operations which are carried out When the lesion is confined to a single toe it is often possible to carry out a local amputation but in certain cases it is wise to amputate all the toes at once If the stump does not heal in about two weeks then it is unlikely to do so and it is probably not justifiable to rest the patient in bed longer than that period of time and it is best to mobilize him as this is occasionally followed by healing Much more commonly in these cases it becomes obvious that a more extensive amputation is required Trans metatarsal amputation and Syme s amputation have been tried but the most satisfactory procedure is below knee amputation An arterial block at the level of the femoral artery should be the only indication for primary above knee amputation Oakley Catterall and Martin (1956) believe that the most satisfactory technique for performing below knee amputation is to use the technique advocated by Silbert (1944) which avoids any form of primary suture at the time of operation instead the stump flaps are loosely wrapped in vaseline gauze and the stump immobilized in a plaster slab for ten days Re dressing is then carried out in the theatre and if there is no sepsis it may be permissible to perform secondary suture More often it is wiser to allow healing by first intention re dressing at ten day intervals until healing is complete Attempts at primary suture have been found

to result in many cases requiring above knee amputation whereas this is practically never necessary in the above procedure

Neuropathic Lesions It is important to recognize the early signs of neuropathic lesions on the feet and in this respect the scaling skin and clawing of the toes have already been mentioned At first the clawing is mobile and can be corrected by the insertion of an appropriate fitting in the shoe When this deformity is fixed however it is essential to avoid any internal fitting as this would merely force the flexed toes against the inside of the shoe and precipitate the development of a pressure sore and later a perforating ulcer In these cases an outside rocking bar may be fitted to the instep Trophic ulcers may occasionally heal when pressure is taken off them and any infection treated and neuropathic joint changes in the tarsus may sometimes be arrested by immobilization in plaster Unfortunately however in a number of cases the destruction of the tarsus is progressive and when this occurs the foot may become so swollen and deformed that the patient may eventually seek amputation himself

General Measures Although the management of each diabetic foot lesion varies according to its aetiology there are certain general principles which may be applied to every case

It is important to establish and maintain good diabetic control and the addition of vitamins may be beneficial In particular the patient with neuropathy may be given added vitamin B in concentrated form such as Parentrovite although there is little evidence that this confers any real benefit When nursing diabetic patients with lesions on their feet it is vital to appreciate that diabetic feet are abnormally vulnerable to minor degrees of trauma and it is essential to try and prevent further lesions developing particularly on the toes or the heel either of the same foot or of the other foot The most satisfactory prophylactic measure in this respect is to nurse the patient with his foot in slings thus keeping the toes off the bed Heel rings are not satisfactory as they create pressure points and great care should be exercised in moving bed cradles so that the feet or the legs

are not struck by a metal part of the cradle Cooling the affected part to room temperature while warming the rest of the feet to promote reflex dilatation and the use of alcohol taken to relieve pain by vasodilation and to aid the collateral circulation are advocated by Rob (1956)

Prophylaxis The management of fully established lesions on the feet of diabetics is so difficult that it is important to stress the need for the most energetic prophylactic measures because many lesions are preventable Good diabetic control reduces the likelihood of infection and may delay the development of arteriosclerosis and neuropathy At the same time diabetics must always pay special attention to the care of their feet and this is even more necessary whenever signs of vascular insufficiency or neuropathy have appeared The importance of foot hygiene has been summarized by Lowrie Redfern and Brush (1955)

The points may be summarized as follows

(1) Foot bathing The feet should be bathed daily avoiding excessive soap to preserve the natural oil The skin may be kept soft with oil or lanoline

(2) Socks or stockings should be one half an inch longer than the feet to avoid binding the toes together

(3) Shoes These should be wide to permit toe movement and ventilation and there should be one half inch space beyond the great toe The lining should be smooth and shoes should be changed daily New shoes should only be worn one hour at a time for breaking in Shoe nails should be avoided *and patients should not walk bare foot*

(4) Every effort should be made to avoid foot injuries and infections Toe nails should be trimmed straight across but not too short Any interdigital tinea should be treated urgently because inter digital infection often starts in this way No hot water bottles or electric pads should be used and no strong antiseptics should be applied to the feet No corn plasters should be applied as they tend to cause pressure and the paring of corns should be done with the utmost care In particular any patient going to a chiropodist should inform him he is a diabetic Corns should be softened and trimmed and callouses should be prevented if possible by

the wearing of well fitting footwear or treated by paring after softening Hard callous being one of the most common causes of subsequent ulceration and cellulitis

The importance of the prophylaxis of these foot lesions is stressed especially in view of the duration of these complications Apart from the importance of such prophylaxis to the patient himself the question is of wider economic importance in view of the long periods of disability which may occur and the long periods of hospitalization which may be required Th Committee on diabetes of the Massachusetts Medical Society (1955) report that the average duration of hospital stay of 50 diabetics with foot lesions was 26 6 days and omitting the short stays was 30 days 90 of the patients were in hospital 60-100 days

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CHAPTER XIII

DIABETIC NEUROPATHY

It is now well recognized that diabetes may be complicated by neurological changes

Marchal de Calvi (1864) was one of the earliest to report neurological symptoms and signs in diabetes mellitus he wrote of pains of sciatic distribution and peripheral areas of anaesthesia Bouchard (1884) observed that in diabetic patients the deep reflexes were often absent Pavy (1885) described lightning pains exquisite paraesthesiae and the nocturnal intensifications of such symptoms and Althaus (1885) commented on the similarity of diabetic neuropathy in some cases to tabes dorsalis

Since these early descriptions many workers have studied the neurological findings in diabetes and it is clear that the manifestations of diabetic neuropathy are manifold Rundles (1945) has emphasized that the entire nervous system may be involved including the central peripheral and autonomic parts but with the incidence chiefly on the peripheral Thus, sensory disturbances are the commonest symptoms with muscle cramps numbness tingling burning sensations and shooting pains—these symptoms being characteristically most severe at night Other disturbances include muscular paresis, autonomic involvement causing sphincter disturbances, and occasionally involvement of the central nervous system with mental changes

Many attempts have been made to classify the diabetic neuropathies Jordan (1936) suggested that there are three main types (1) hyperglycaemic in which muscle tenderness is found at the time of diagnosis and clears when the diabetic state is brought under control (2) degenerative in which there is obvious circulatory impairment usually with other signs of degenerative cardiovascular disease and in which often the only finding is the absence of reflexes and (3) neuritic which is perhaps the best recognized though by no

means the commonest form of diabetic neuropathy and is characterised by pain paraesthesiae and pareses In this neuritic type many workers including Rudy and Epstein (1945) and Rundles (1945) have observed that the symptoms may first appear or become aggravated after the control of the diabetic state

Martin (1953) has thoroughly reviewed the literature on the subject of diabetic neuropathy and has put forward certain views on its causation

Degenerative vascular disease vitamin B_1 deficiency and the disordered metabolism of diabetes are the three major factors commonly cited. Martin carried out skin temperature studies and took oscillometric readings of the pulsations in the calves in 150 patients with diabetic neuropathy and the results of his tests did not suggest that vascular disease is of importance in the aetiology of the condition nor is there any conclusive evidence that it is caused by an absolute relative or conditioned B_1 avitaminosis

Poor diabetic control would appear to be a more definite causal factor in the development of neuropathy and Martin found that diabetic neuropathy was rare in diabetics who had always been well controlled Gilliland (1951) considered that diabetic neuropathy occurred as part of the Kimmelstiel Wilson syndrome Martin was unable to support this belief and considered that the association of diabetic peripheral nerve disease and the Kimmelstiel Wilson syndrome was coincidental Diabetic neuropathy seems to be mainly related to neglect of diabetic treatment while diabetic retinopathy and nephropathy are more closely related to the duration of the diabetic state The co existence of these three degenerative complications of diabetes mellitus in some cases is explained by the assumption that they are all in some as yet ill explained way the result of the metabolic disorder

Clinical Manifestations of Neuropathy

Hyperglycaemic Neuropathy It is common for pain and paraesthesiae to be present at the onset of severe diabetes *coincidentally with hyperglycaemia In these cases there*

may be no objective signs but the reflexes are sometimes diminished or absent The condition is rapidly relieved by diabetic control

Frank Neuropathy This group includes a large number of cases presenting a variety of symptoms and associated with definite objective signs

Symptoms

Pain This is the most outstanding symptom It is described by the patient as cramp like burning or tingling and is almost invariably worse at night The intensity may be extreme and response to analgesics poor The pain most frequently affects the legs and feet but it is often ill defined and ill localized with occasional bursts of shooting or lightning stabs These symptoms have sometimes been described by the term electric feet syndrome

Weakness Patients complain of weakness much less commonly than of pain but weakness and wasting of the quadriceps femoris muscle is not uncommon and foot drop is also sometimes seen (Hirson Feinmann and Wade 1953)

Physical Signs Absent tendon reflexes are the most commonly met signs in diabetic neuropathy and Martin found some reflex abnormality in 92 per cent of the cases in his series

Hypalgesia to pin prick and cotton wool is also common and vibration sense is frequently lost in the legs and muscle tenderness is present in about half of the cases Motor signs are less common but in those cases complaining of muscle weakness there is usually some wasting present An interesting feature of the symptoms and signs in diabetic neuropathy is that they are asymmetrical

Other Manifestations Apart from these more usual symptoms and signs in diabetic neuropathy there are a number of less commonly encountered manifestations

Neuropathic Lesions of the Feet Perforating ulcers of the feet are common in diabetics with neuropathy Frequently the lesion is painless and the patient often ignores it until secondary infection occurs and even osteomyelitis of the underlying bone develops In its most advanced form the

neuropathic lesion of the foot can result in what is virtually a Charcot joint. This complication of diabetes was first described by Bailey and Root (1942 1947) who observed the painless destruction of the tarsus in 17 patients with poorly controlled diabetes Foster and Bassett (1947) described two cases of severe and poorly controlled diabetes with signs of damage to the somatic and nervous system in the region of the neuropathic joints in the lower limbs Martin found evidence of neuropathic bone and joint lesions in 6 per cent of his cases and suggested that these changes occur more frequently than has previously been recognized

The tarsus is most commonly affected as in the case reported by Lister and Maudsley (1951) but similar changes have been observed in the knee joint (Shore 1947 Spear 1947) and in the ankle joint (Foster and Bassett 1947) A Charcot joint may develop rapidly in diabetic neuropathy with sudden swelling of the foot in the absence of infection The prognosis of the neuropathic arthropathy appears to be bad and there is little tendency to improvement Amputation is often required See also Chap XII

Gastro intestinal Disturbances Nocturnal attacks of diarrhoea have frequently been reported in patients with diabetic peripheral nerve disease The patient is usually awoken in the early morning with a bout of diarrhoea lasting a few hours the bouts may occur almost daily for a period and may then be followed by a period of constipation Lower abdominal discomfort and flatulence are the symptoms most commonly associated with the diarrhoea The stools are loose but otherwise no macroscopic nor microscopic changes are present Barium studies and sigmoidoscopy are likewise normal It has been assumed that the irritability of the bowel is a manifestation of diabetic neuropathy affecting the autonomic nervous system Bargen Bollman and Kepler (1936) referred to the condition as the diarrhoea of diabetes and Sheridan and Bailey (1946) reported a series of 40 cases A barium meal was carried out in 28 cases and found to be normal proctoscopy was normal in 15 cases studied but histamine fast achlorhydria was present in 14 of 29 patients Hydrochloric acid produced little benefit but

crude liver extract by injection was of value in controlling the diarrhoea in a number of the cases

Urogenital Disturbances Impotence occurs occasionally in diabetes and in particular Rundles (1945) has stressed that it is common in patients with diabetic neuropathy He found it in 27 5 of his male cases

Disturbance of bladder function may also occur—the commonest clinical picture being that of retention with overflow in the absence of any evidence of bladder neck obstruction

It is probable that both impotence and retention with overflow may be dependent upon neuropathy affecting the sacral autonomic nerves

Diabetic Myelopathy Garland and Tavener (1953) have described five cases of diabetic neuropathy in which there were no objective sensory changes but all of whom complained of pain in the legs maximally in the hip and thigh All showed some degree of wasting of the leg muscles with loss of tendon reflexes and in four of the five cases the C S F protein was raised Electromyography was performed on four cases and in each case the findings were compatible with a cord lesion The authors point that the peripheral site of the lesion in diabetic neuropathy has been accepted for many years although there are a number of references to cord lesions in the literature Bruns (1890) described motor disturbances without objective sensory loss chromatolysis of anterior horn cells and degenerative changes in the posterior roots are mentioned by Courville (1945) Griggs and Olsen (1937) found degenerative lesions of the posterior and lateral columns in the cervical and mid thoracic regions of the cord Woltman and Wilder (1929) found similar changes

Other manifestations of diabetic neuropathy have also been described Pupillary changes are frequently found in cases of diabetic neuropathy The commonest abnormality is a sluggish reaction to light but although many writers have described the Argyll Robertson pupil as occurring in diabetes it is only rarely seen Cranial-nerve palsies are common in diabetics but the evidence would suggest that they

are more commonly due to cerebral arterio clerosis rather than to a primary nerve lesion

Although diabetic persons are perhaps no more frequently affected with degenerative changes in the cervical or lumbar discs they do seem rather more liable to suffer symptoms from root compression than non diabetics Sciatic pain and the pain of cervical radiculitis are thus common in diabetic patients

The treatment of all forms of diabetic neuropathy remains unsatisfactory Cytamen pregnant mammalian liver vitamin B complexes and other preparations have all been tried with no conclusively satisfactory results Good diabetic control at present seems to be the only practical approach

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lying cause remains unknown Many factors have however been considered

I Size of the Foetus

The infants born to diabetic mothers are often abnormally large and this naturally presents an increased hazard to the infant at the time of delivery The cause of these infants being so large is not fully understood but the causative factor operates not only in frankly diabetic women but also in cases of prediabetics because an enquiry into the obstetric history of women presenting with diabetes in later life will often reveal that they were delivered of abnormally heavy infants many years before the onset of frank diabetic symptoms Barns and Morgans (1948) have suggested that there might be an excess of growth hormone from the maternal anterior pituitary lobe causing the infant both of the diabetic and of the prediabetic mother to be large

II Late Toxaemia of Pregnancy

Toxaemia late in pregnancy is more common in diabetic than in non diabetic women and this is certainly a contributary factor in the high foetal mortality in these pregnancies Hurwitz and Higano (1952) found that 29 per cent of diabetic women developed toxaemia in pregnancy compared with 8 per cent of non diabetic women They were able to relate the incidence of toxaemia directly to the severity of the diabetes and also noted a higher incidence when the diabetes was of long duration Barns and Morgans (1940) using very strict criteria for diagnosing toxaemia at University College Hospital found that 43 per cent of diabetic women developed toxaemia compared with 35 per cent of non diabetic women but they believe that diabetics have a tendency to develop a severe type of toxaemia

Peel and Oakley (1949) stressed that the greater incidence of toxaemia falls in the last three weeks of pregnancy

Smith *et al* (1944) found that in the late toxaemia of pregnancy there is often a high level of serum gonadotrophin a low serum oestrin level and diminished pregnandiol excretion Furthermore these hormonal abnormalities were shown to

CHAPTER XIV

DIABETES AND PREGNANCY

In the pre insulin era it was rare for a diabetic woman to become pregnant and when pregnancy did occur the maternal mortality rate was high Amenorrhoea is common in uncontrolled diabetes and this was probably the factor accounting for the low fertility rate in untreated diabetic women figures ranging from 2–6 per cent being quoted by Von Noorden (1909) and Skipper (1933) Furthermore in the pre insulin era the immediate maternal mortality in pregnant diabetic women varied from 25–30 per cent (Duncan 1882 Williams 1909) and many more women died within two years of delivery usually in diabetic coma

Since the introduction of insulin the fertility rate has risen steadily and the association of pregnancy and diabetes is now so common in diabetic practice that it is essential for those undertaking the care of diabetics to be familiar with the management of these cases

With proper diabetic care the maternal mortality rate has fallen to very low figures Lawrence and Oakley (1942) quoted a mortality rate of less than 2 per cent and in the Joslin Clinic (1952) there have only been 3 deaths among 702 cases observed since 1922 The introduction of insulin has thus resulted in pregnancy being virtually no more of a hazard to the diabetic than to the non diabetic woman On the other hand the chances of the foetus surviving are still far from certain Henley (1947) in reviewing 160 pregnancies which occurred in diabetic women in the pre insulin era found a foetal survival rate of 57 per cent Comparing this with present day figures he found that the foetal loss rate is still as high as 40 per cent in many centres and few workers until recently consistently claim a foetal salvage rate of more than 70 per cent Intrauterine deaths still births and neonatal deaths account for the actual foetal losses but the under

doubtful whether it is ever a cause of neo natal death and there is no indication that the administration of glucose by mouth is of the slightest value to these infants

IV Congenital Abnormalities in the Foetus

The incidence of congenital abnormalities is greater in children of diabetic than of non diabetic mothers and this of course causes an increased mortality rate Comyns Berkeley *et al* (1938) state that the incidence of congenital abnormalities in general is 3 per cent whereas Barns and Morgans (1949) found an incidence of 10 per cent in a series of 40 diabetic pregnancies Hydramnios is frequently present when the foetus is abnormal

In a series of 14? cases born to diabetic mothers at King s College Hospital Peel and Oakley (1949) found 9 cases of gross congenital abnormalities giving an incidence of 6 3 per cent Internal hydrocephalus congenital heart disease imperforate anus renal tract abnormalities and skeletal deformities were all found Furthermore Whittaker (1956) found on inviting a group of diabetic mothers who had been delivered at King s College Hospital to bring their children for examination that 10 per cent of these children had evidence of some gross congenital abnormality

Management of the Pregnant Diabetic Although some pregnancies in diabetes may proceed normally and result in the delivery of normal infants at full term it is not possible to determine the cases in which this is likely to occur with any degree of accuracy A previously normal obstetric history is probably the best prognostic sign in this respect but it is by no means always reliable

Because of the persisting high foetal loss rate it is essential to regard every diabetic pregnancy as being potentially abnormal and requiring special attention throughout the pregnancy with the fullest co operation between the physician the obstetrician and the paediatrician The physician must be constantly aware of the effect that the pregnancy may have on the diabetic state and the obstetrician must consider the effects that diabetes may have upon pregnancy

precede the onset of the toxaemia On the assumption that these abnormalities might be related to the foetal catastrophes White *et al* (1939 1947) treated a series of pregnant diabetic women with oestrogens in large dosage They claimed a much higher foetal salvage rate after the introduction of this form of treatment but no strictly comparable control cases were studied No other workers have been satisfied that hormone therapy is of any real value and in a Medical Research Council Report (1955) it was concluded that oral stilboestrol and ethisterone did not reduce the foetal mortality and there was little if any beneficial effect on maternal health in pregnancy

III Hypoglycaemia in the Newborn

The normal blood sugar level in infants is much lower than in adults Ketteringham and Austin (1938) found in a series of normal infants born to non diabetic mothers that the mean fasting blood sugar level fell to the normal infant range which is 55–75 mg per 100 ml during the first two days Much lower figures have been found both in infants of diabetic and of non diabetic women and Pedersen (1954) quoted a range for babies of non diabetic mothers of 26–150 mg per 100 ml and for babies of diabetic mothers 20–205 mg per 100 ml but in both groups the values ranged mainly from 40–90 mg per 100 ml In this series the average blood sugar in normal infants was 66 mg per 100 ml and in infants of diabetics it was 63 mg per 100 ml the difference not being significant

In the case of pregnant diabetic women the blood sugar of the infant is likely to be high at the time of birth unless the maternal diabetes is very well controlled The fall to normal level after delivery is therefore greater in these infants than in those born to non diabetic mothers and it has been thought that they may sometimes suffer from the effects of hypoglycaemia Pedersen (1954) found a direct relationship between the blood sugar of the mother and infant at birth but found that the subsequent fall in the blood sugar of the infant is rapid and may occur within half an hour of birth This rapid fall in blood sugar is the only factor likely to cause serious harm to the infant of the diabetic but it is very

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Management of the Pregnant Diabetic Although some pregnancies in diabetes may proceed normally and result in the delivery of normal infants at full term it is not possible to determine the cases in which this is likely to occur with any degree of accuracy A previously normal obstetric history is probably the best prognostic sign in this respect but it is by no means always reliable

Because of the persisting high foetal loss rate it is essential to regard every diabetic pregnancy as being potentially abnormal and requiring special attention throughout the pregnancy with the fullest co operation between the physician the obstetrician and the paediatrician The physician must be constantly aware of the effect that the pregnancy may have on the diabetic state and the obstetrician must consider the effects that diabetes may have upon pregnancy

In the light of our present experience the highest foetal salvage rates have been reported from centres where the fullest co operation has been practised between the physician obstetrician and the paediatrician and where the infant has been delivered during the last four weeks of pregnancy either by Caesarean section or by surgical induction Adams (1955) gives a comparison of mortality rates before and after close liason between internists and obstetricians was instituted the gross foetal mortality was reduced from 40–14 per cent intrauterine deaths from 27–5 per cent and the neonatal deaths from 13–9 per cent Together the physician and the obstetrician must decide in each individual case at what stage and by what means the pregnancy is to be terminated The help of the paediatrician is vital in preventing an improved foetal salvage rate being adversely balanced by an increased neonatal death rate

It is convenient to consider the problems that may arise in each trimester of pregnancy

First Trimester When a diabetic woman becomes pregnant she should be told that the pregnancy causes no particular risk for herself so long as she remains under close supervision and that everything possible will be done to ensure the delivery of a healthy child although this must be a less certain outcome of the pregnancy than were she not diabetic It is well to explain at this stage that the pregnancy will probably have to be terminated before full term either by the premature induction of labour or by Caesarean section

Regular monthly attendance at the diabetic clinic and at the antenatal clinic must be insisted upon at the outset with more frequent attendance later

In the first trimester of pregnancy there may be a slight increase in the insulin requirements but unless hyperemesis precipitates ketosis which requires treating on its own merits there is not usually any marked increase until later in pregnancy (Skipper 1933 Barns and Morgans 1949) Throughout pregnancy however there is a lowering of the renal threshold for sugar and this presents a constant difficulty Blood sugar estimations are essential for assessing diabetic

control and raising the insulin dose simply because of increased glycosuria and without blood sugar control may easily cause hypoglycaemia

Routine antenatal examination is carried out at this stage as in any other case with special reference to any previous obstetric history Blood examinations including W R and Rhesus factor determination should be carried out and it is wise to be sure that the patient has had a recent chest X ray

Second Trimester The diabetic state is usually fairly stable during this period but again it must be assessed by blood sugar estimation rather than by the degree of glycosuria present In the antenatal clinic a close watch must be kept for any early evidence of toxaemia the urine blood pressure and weight records being the chief factors on which this can be assessed

Third Trimester It is during the last three months of pregnancy that the closest observation of the pregnant diabetic woman is required Toxaemia of pregnancy hydramnios premature labour and intra uterine death are all liable to occur at this stage while the insulin requirements tend to increase and the diabetic control becomes more difficult

The patient must therefore attend both the diabetic clinic and the antenatal clinic much more frequently and during the latter part of the time she should be seen each week Ideally she should be admitted to hospital for full assessment at the 35th week (Tolstoi 1953) The physician and the obstetrician can then decide on when the pregnancy is to be terminated and by what method

Routine delivery by Caesarean section at 36 weeks will result in a high proportion of live births But this may mean subjecting a number of women unnecessarily to Caesarean section and it may result in a number of infants suffering neonatal deaths although these may be infants who would otherwise have died in utero On the other hand although it seems as if pregnancy can be continued until about the 38th week when the chances of a live birth and a viable infant are optimum a certain number of infants will then die in utero between the 36th and the 38th week if pregnancy is allowed to continue until then It is thus not possible to

dogmatize on either the time or the method of delivery and each case must be considered on its own merits

For the obstetrician the exact time of the termination of pregnancy depends upon his assessment of the maturity and the size of the foetus the presence or absence of toxaemia or hydramnios and a consideration of the previous obstetric history

For the physician the state of the diabetic control and his assessment of the patient s general physical condition are the chief factors to be considered

Caesarean section is probably the method of delivery which gives the most consistently good results although there has been an increasing tendency of late to induce labour surgically at any rate as a trial Caesarean section being performed only in those cases where there is a definite obstetric indication for this method (Hurwitz and Higano 1952 Tolstoi 1953)

From the point of view of managing the diabetic state over the time of delivery it is probably easier for the physician when a Caesarean section is performed The time can usually be chosen and the carbohydrate intake and insulin cover can be planned as in the case of any other surgical operation (See Chap XVII) Soluble insulin should be used rather than any long acting preparation and it is esseential to ensure that the patient s stomach is empty even of glucose drinks when she goes to the theatre The intravenous route must be used for the administration of appropriate amounts of glucose in 50 per cent solution Immediately after delivery there is often a dramatic fall in the patient s insulin requirement and this must be watched for so that hypoglycaemia may be avoided either by reducing the insulin dosage or increasing the carbohydrate content of the diet If possible the diabetic state should be controlled by blood sugar estimations over this period

Care of the Infant

The infants of diabetic mothers have a high neonatal mortality They are frequently large and unhealthy looking often having a brawny generalized oedema Intracranial

haemorrhage is common at birth and there is a high incidence of atelectasis with respiratory distress (Tolstoi 1953) It has been shown by Winter and Gellis (1954) that the respiratory distress is due to the development of pulmonary hyaline membranes throughout the lungs causing a diffuse type of atelectasis This was found in 75 per cent of infants lacking some other major cause of death The cause of the membrane is not clear but the child develops increasing respiratory distress during the first few hours of life and either dies of respiratory failure after twenty four or seventy two hours or gradually begins to improve and recovers completely over the same period of time

The incidence of pulmonary hyaline membranes is higher in infants born of diabetic mothers than in other infants and it is more common in all infants delivered by Caesarean section than in those delivered by the pelvic route White (1954) found hyaline membranes in 85 per cent of autopsied infants of diabetic mothers The choice of Caesarean section delivery in infants of diabetic mothers is therefore not ideal but the high foetal death rate in such infants justified the increased risk of pulmonary hyaline membranes from Caesarean section delivery Bound *et al* (1956) found that 30 of 36 babies with the pulmonary syndrome of the newborn were premature and a hyaline membrane was present in 73 per cent

In order to reduce the neonatal mortality of these infants to a minimum their care should be entrusted to the paediatrician as soon as they are delivered In spite of their large size these infants must be treated as premature babies The airway must be cleared and postural drainage instituted but only for as long as is essential because the viscera often being enlarged may cause further respiratory embarrassment by their pressure on the diaphragm Oxygen should be given if respirations are delayed stomach aspiration should be carried out since these infants frequently have excessive amounts of fluid in the stomach and subsequent vomiting and aspiration of the material may favour the development of the hyaline membrane syndrome (Gellis *et al* 1949) This may be repeated as necessary The infant should then

be moved to a special nursery and placed immediately in an incubator in a humidified oxygen environment for 24 hours or longer Pennoyer and Hartman (1955) They should not be bathed and feeding witheld for the first forty eight hours Antibiotic therapy should be started

The onset of hyaline membrane disease may be preceded by apnoea cyanosis abnormal respiration or chest retraction soon after delivery but more commonly rapid respirations with a constant expiratory grunt retraction of the lower chest and sometimes intercostal spaces fullness and prominence of the sternum flaring of alae nasi restlessness proceeding to fatigue and exhaustion increasing cyanosis and periods of apnoea increasing in severity come on gradually over a period of 4-6 hours increasing in severity and either resolving completely (1-4 days) or terminating fatally (Pennoyer and Hartman 1955)

It is clear that there is still much to be learnt about the management of diabetes and pregnancy In the light of our present state of knowledge it cannot be overemphasized that it is essential that the physician the obstetrician and the paediatrican should co operate in the closest way possible and that the patient should be under observation throughout the entire pregnancy The satisfactory results that can be achieved with such an approach have been stressed by Pedersen *et al* (1954) In 149 diabetic pregnancies there was an overall foetal mortality of 27 per cent On dividing the patients into long and short term treated diabetics according to the stage of pregnancy when the patient was first seen he found that the foetal mortality was only 12 per cent in the cases followed from early pregnancy compared with 36 per cent in the cases which did not come under observation until the latter part of pregnancy All cases were treated on the same lines the principles being classical control of the diabetes with conservative and obstetrical management only 8 per cent cases being delivered by Caesarean section No hormones were administered and all the infants were fasted for at least twenty four hours after delivery Pedersen believes that the striking difference in foetal mortality in the two groups is good evidence that the most important single

factor in the management of the pregnant diabetic is the exercise of strict diabetic control throughout the whole of the pregnancy

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CHAPTER XI

PREDIABETES

THERE are many indications that a disordered carbohydrate metabolism may exist for many years before frank diabetic symptoms develop and the diagnosis is conclusively established. Thus many patients present with conditions which have come to be regarded as being associated with diabetes of long duration. In particular patients are not infrequently found to be diabetic when they present with diabetic retinopathy which is believed to develop only after the diabetic state has existed for upwards of ten years. Similarly a patient may present with oedema and albuminuria and glycosuria and a diagnosis of diabetic nephropathy is made—this again being a later complication of diabetes. It must be assumed in these cases that for many years the diabetic state has been so mild that no characteristic diabetic symptoms have developed.

It is however when one inquires into the obstetric history of women developing diabetes in later life that the most conclusive evidence of the existence of a prediabetic syndrome is forthcoming. It is common experience to find that women presenting in diabetic clinics in middle age have borne excessively heavy babies many years previously and have not infrequently lost infants by premature birth or neo-natal death. Many workers have been able to confirm that the birth weight of infants born of women who subsequently develop diabetes tends to be greater than normal and the total foetal mortality in such pregnancies is higher than is usual in non diabetic pregnancies (Miller 1945, Barns and Morgans 1948, Jackson and Woolf 1956).

Indeed Jackson (1952) discovered a considerable number of unsuspected cases of diabetes by carrying out glucose tolerance tests on mothers who were delivered in hospital of babies weighing over 10 lbs.

The precise meaning of the prediabetic state is still not

fully understood and the specific cause for foetal enlarge ment and mortality are unknown It has however been suggested that there is an increased output of growth hor mone by the anterior pituitary during pregnancy and that this may be responsible for the large size of the foetus and occasionally for its intra uterine death (Teel 1026 Engle and Mermod 1928) In any event from the practical stand point it is important to recognise that infants born to women in the prediabetic phase are liable to the same ob stetric hazards as are those of frankly diabetic women and secondly a woman who is delivered of infants weighing more than 10 lb should be investigated to exclude the possibility of her having latent diabetes

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CHAPTER XVI

THE TUBERCULOUS DIABETIC

INCIDENCE

THE prevalence of pulmonary tuberculosis is greater in diabetics than in the general population and before the discovery of insulin active pulmonary tuberculosis was a common autopsy finding in diabetics (Griesinger 1859 Windle 1883 *Williamson 1898*)

It is difficult to determine the true incidence of tuberculosis in diabetics because different criteria are adopted in different surveys Thus in an extensive public health investigation carried out in Philadelphia there was an incidence of *pulmonary tubercle in 8 4* per cent of *3 106* diabetics as compared with an incidence of 4 3 per cent of 70 767 non diabetic industrial workers (Dillon *et al* 1952) On the other hand Warwick (1957) found an incidence of only 1 8 per cent in 1 851 diabetics observed at University College Hospital over the years 1940–54 The table reproduced from her paper summarizes the findings of some of the larger surveys carried out (Table 1)

The incidence of tuberculosis in diabetics has clearly been influenced by the better diabetic control which has been achieved since the advent of insulin and *Himsworth (1938)* claimed that well controlled diabetics were no more liable to develop pulmonary tubercle than non diabetic subjects

This view has not been full borne out but in the Philadelphia survey it was found that the prevalence of active tuberculosis increased markedly with the severity of the disease Furthermore active pulmonary tuberculosis was more common in patients under 40 than in older cases and there was also an increased prevalence in those young patients who had been diabetic for ten years or more

Warwick found the same relationships between age control and duration of diabetes She also found that in nearly

all age groups under 65 there was a greater prevalence of tuberculosis among diabetic women than in diabetic men. Over 65 years of age the male diabetics appear to show an increased prevalence of tuberculosis compared with the control group but no appreciable difference was shown amongst the women. It also appears that the underweight diabetic is more liable to pulmonary diabetes than the obese patient.

Table 1 INCIDENCE OF TUBERCULOSIS OBTAINED FROM DIABETIC CLINICS USING ROUTINE RADIOGRAPHY

After Warwick M T (1957) *Quart J Med* 26 31

Authors	Date	Total		Diabetic patients: Pulmonary tuberculosis Number	per cent
Steidl and Sosman	1927	135		16	9
Adams	1929	1 000		10	1
Root	1934	1 659		4	2 8
Himsworth	1938	230		15	6 5
Root and Bloor	1939	364		11*	3
Boucot Cooper Dillon Meier and Richardson	1952	3 106	(total)	261	8 4
			(active)	80	2 6
Present series	1956	1 851	(active)	34	1 8

* Figure calculated from percentage given in the report

PATHOLOGY

There has been an impression among clinicians that when pulmonary tuberculosis occurs in diabetics the progress of the disease is rapid and associated with early caseation and a tendency to generalized spread with a poor fibrotic reaction. Hyperglycaemia, acidosis, increased glycerol production, altered function of the leucocytes and tissues and lowered pulmonary concentration of phospholipids and lipids have all been advanced as possible causes for the diabetics susceptibilities and poor resistance to tubercle but no satisfactory explanation has been offered (Ferrara 1952)

Radiological Appearances

The X ray appearances often show advanced changes when pulmonary tuberculosis is first diagnosed Warwick



Fig XVI 1 —Tuberculosis in a diabetic woman aged 70

found in her series of 108 tuberculous diabetics that at the time of diagnosis 25 per cent of cases had lesions in one zone only 35 per cent had lesions in more than two zones and 48 per cent had cavities Steidl and Sosman (1927) recognized a

specific radiological lesions which they described as dia betic tuberculosis This is characterized by a wedge shaped lesion spreading from the hilum and occurring in dia betics over the age of 40 years Fig XVI 1 shows the



Fig XVI 2 —Same case aft t eatment

X ray appearances in a diabetic woman aged 70 Fig XVI 2 shows the satisfactory improvement on antibiotic therapy Warwick found this lesion in 11 per cent of her ca es but only six were over the age of 40 and she considered that it

was not possible to recognize any specific radiologica features in the tuberculous diabetic

MANAGEMENT

The management of the tuberculous diabetic may be summarized by stating that each condition must be treated vigorously on its own merits

I Diabetic Control It is of the utmost importance to maintain good diabetic control This is often rendered difficult first because the diabetes may become more severe in the presence of active tuberculosis and secondly because the treatment of the latter may require a high calorie diet and an

Table 2 MORTALITY RATE IN TUBERCULOUS DIABETICS

After Luntz G R W N (1957) *Brit med J* 1 1085

Author	No of Cases	Period of Observation	Mortality No	Mortality per cent
Fitz (1930)	35	3 years	6	74
Lorenzen (1931)	116	3	96	82
Kennedy (1933)	41	2	1	51
Root (1934)	245	3	160	65
Myers and McKean (1935)	80	1½	35	44
Wiener and Kavee (1936)	218	2	102	47
Himsworth (1938)	29	5 12 4	6	21
Mark *et al* (1942)	349	5	115	33
Banyai and Cadden (1944)	115	Not stated	6	58
Poulsen (1946)	100	5	91	91
Gauld and Lyall (1947)	1	3	11	65
Lawrence and Whittaker (1948	110	Not stated	39	35
Ferrara (195)	53	4	29	55
Munkner (1953)	15	2	9	60
Jacobs *et al* (1953)	55	4	35	100
Gass (1953)	100	5	24	24
Thosteson and Tibbetts (1953)	294	5½	171	58
Reaud (1953)	38	½	4	11
Total	2 010		1 061	53

increased carbohydrate allowance For these reasons it is wise to treat the patient with two or more doses of soluble insulin each day

2 **Control of Pulmonary Tuberculosis** The introduction of effective antibacterial therapy for pulmonary tuberculosis has been of great benefit to the tuberculous diabetic Thus in Warwick s series no diabetic with pulmonary tuberculosis receiving antibacterial drug treatment since 1950 has died from tuberculosis Rest antibacterial therapy with streptomycin para amino salicylic acid (P A S) and isoniazid (I N A H) in their various combinations and any local collapse therapy required are the initial measures in the treatment of pulmonary tuberculosis in diabetics Should any form of thoracic surgery be required such as segmental resection lobectomy pneumonectomy or thoracoplasty these procedures may be carried out under the cover of an antibiotic umbrella

Although ideally the tuberculous diabetic should be treated in a special unit the importance of this has only recently been appreciated Luntz (1957) has described the work of such a unit which was introduced in Birmingham The unit comprises 25 beds with out patient clinics and provides domiciliary services and has greatly improved the standard of treatment offered to tuberculous diabetics

PROGNOSIS

The combination of diabetes and pulmonary tuberculosis has in the past been a particularly serious one (see Table -) but this should now be regarded as out dated and a much more optimistic view may be taken when a case presents although the management of the case calls for the closest co-operation between the chest physician and those in charge of the diabetic aspects of the case

PROPHYLAXIS AND EARLY DIAGNOSIS

It is more common for tuberculosis to develop in known diabetics than for the reverse to occur—or for the two conditions to present simultaneously Routine chest X rays should be carried out on all newly diagnosed diabetics and

further X rays should be included as part of the annual re assessment to which all patients attending diabetic clinics should be submitted

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CHAPTER XVII

SURGERY AND ANAESTHESIA IN DIABETICS

A SURGICAL operation may be an incident in the life of a diabetic just as in the case of non diabetics but in the light of modern surgical technique modern anaesthetic procedures and available antibiotics the operation and anaesthetic risk should rarely be greater for the diabetic than for the non diabetic On the other hand the control of the diabetic requires careful supervision over the period of an operation firstly because the diabetes may have become unstable on account of the condition especially when this has been a septic lesion necessitating surgery and secondly because there is often a temporary period of instability following surgery although modern anaesthetics in themselves are rarely the cause of severe ketosis which sometimes used to follow the administration of ether On the other hand the stress of all the circumstances associated with an operation may be sufficiently sympathetico mimetic to cause a release of adrenaline and consequent hyperglycaemia

The diabetic complications most frequently requiring surgical treatment are those lesions of the feet which eventually necessitate amputation while other septic lesions such as carbuncles and ischio rectal abscesses may require drainage under general anaesthesia At the same time the diabetic is liable to all of the normal hazards of life and may be required to undergo planned surgical procedures such as cholecystectomy partial gastrectomy or routine operations such as tonsillectomy or herniotomy Similarly the pregnant diabetic has frequently to be subjected to a planned Caesarean section as the safest method of delivering her infant When it is possible to carry out such operations to a pre arranged plan there should rarely be any difficulty in the management of the case When however a diabetic presents with an acute surgical emergency it may not be possible

to establish ideal control before operation and a modified technique has to be adopted

MANAGEMENT OF THE PLANNED CASE

It is most satisfactory to admit cases at least three or four days before the operation date During this time the degree of diabetic control can be assessed by urine tests and serial blood sugar estimations and any necessary adjustment in the diet may be made In general it is best to interfere as little as possible with the treatment of a well controlled case but when the patient is taking an appreciable dose of insulin e g more than 20 units daily it is wise to change to two or more doses of soluble insulin because of the greater ease in establishing good 24 hour control with soluble than with any long acting insulin

It is next important to try to have the time of operation arranged as nearly as exactly as possible Ideally the diabetic patient being submitted for a planned operation should be the first case on the list and preferably the list should be in the morning

The pre operative preparation should be simple and should differ very little from that carried out in non diabetics Thus overnight starvation should be the rule and nothing should be given by mouth for at least four hours before operation time The equivalent of the patients normal carbohydrate breakfast content should be given intravenously as 50 per cent glucose together with the pre arranged dose of soluble insulin Oral glucose appears to have a notorious tendency to be present in the stomach when the patient arrives in the theatre and it is for this reason that the above method is preferred There is nothing which exasperates an anaesthetist more than for the patient to vomit and possibly aspirate stomach contents especially when the administration of such fluids has been on the direction of a physician Any further periodic administration of glucose required over the operation period can be similarly given by the intravenous route at normal intervals Blood sugar estimation may be carried out to allay anxiety on the part of the anaesthetist whose frequent concern is lest the patient should

become hypoglycaemic and fail to regain consciousness although this is an extremely rare complication of administering an anaesthetic to a diabetic Except in the case of operations on the alimentary tract and when vomiting persists the post operative patient is usually able to take carbohydrate in fluid form at regular intervals the diabetes being controlled by soluble insulin with periodic blood sugar estimations if there is any difficulty about collecting urine samples If there is any severe degree of ketosis or hyperglycaemia insulin will be required four hourly but this is rarely necessary and the most satisfactory method of re establishing control is by the use of the 6 hourly round the clock method (see p 86) and the majority of cases do not require more than twice daily soluble insulin and are very quickly able to revert to their normal diet and normal insulin preparation and dose In the case of afternoon operations it is usually possible for the patient to have a normal breakfast preceded by a pre arranged dose of soluble insulin It may also be possible for him to take the mid morning snack by mouth so long as this is due more than four hours pre operatively otherwise this snack must be given intravenously as 50 per cent glucose and in any case the equivalent of this patient s normal lunch time carbohydrate must be given by the intravenous route Many anaesthetists will be anxious that the carbohydrate content of this lunch time meal should be greater than the patient s normal lunch and that it should be covered with an extra injection of insulin This should rarely be necessary —the principle to be followed being that the patient s normal stabilization should be interfered with as little as possible Following an afternoon operation the diabetic control can usually be rapidly restored by following the same general principles as those suggested after morning operations In the case of operations on the alimentary tract where nothing is permitted by mouth for perhaps 36–48 hours post operatively it is necessary to use glucose in the intravenous fluid A convenient preparation is 5 per cent glucose saline which then contains 30 gm carbohydrate in each 600 ml bottle On the assumption that 5 or 6 of these

bottles are used each day a reasonable carbohydrate intake is assured and the diabetes can very easily be controlled by 4 or 6 hourly injections of soluble insulin

MANAGEMENT OF THE ACUTE SURGICAL EMERGENCY

It sometimes happens that a new case of diabetes is discovered on routine pre operative urinalysis when the patient is admitted with an acute surgical condition but it is more common for the case to be already a known diabetic In either event the diabetes may well be unstable possibly with severe ketosis The latter should if possible be treated before operation and in any event an immediate blood sugar estimation should be carried out and prompt action taken If the blood sugar is greater than 400 mg per 100 ml with ketones present in the urine it will be quite safe to give 100 units of soluble insulin—50 units intravenously and 50 by a deep subcutaneous injection At the same time an intravenous infusion should be set up with which the patient may be taken to the theatre Initially starting with normal saline the infusion can be changed to 5 per cent glucose when it is established that the blood sugar is coming under control thereafter the diabetic state being controlled by regular injections of insulin with frequent blood sugar estimations

RESPONSIBILITY FOR THE CASE

From the time the patient receives his pre medication until he has fully regained consciousness on his return to the ward the anaesthetist naturally feels responsible for the case and because of this he feels that it is right that he should have a free hand in ordering any treatment to the patient during this period and it is over this point that anaesthetist and physicians sometimes find it difficult to co-operate fully It is however essential that they should do so and that they should take a joint responsibility for the patient over the operation period As already stated the anaesthetist fears hypoglycaemia as the greatest hazard although in fact it is not a common complication during the surgical treatment of diabetics As pointed out by Foster and Francis (1955) there are usually stress factors present in the surgical diabetic

which tend to cause hyperglycaemia These include infection both physical and mental trauma blood loss anoxia while any acute surgical emergency may cause a previously well controlled diabetic to become uncontrolled Admittedly the relief of the surgical condition especially when there is sepsis present may predispose to hypoglycaemia and in the particular case of the termination of pregnancy by Caesarean section there is frequently a sudden fall in the blood sugar and in the insulin requirements of the mother This is however one of the few instances when hypoglycaemia is likely to occur and provided the blood sugar is determined at regular intervals there should be little difficulty in controlling the condition Detection of clinical signs of hypoglycaemia in the unconscious patient may be difficult because most patients are sweating in the heat of the theatre while the pulse rate and volume may vary on account of the operation and the anaesthetic No reliance should be placed on any observation except blood sugar estimations

Choice of Anaesthetic

Apart from avoiding the use of any agent likely to increase the blood sugar levels by releasing glycogen from the liver it is important that the diabetic patient should not be rendered anoxic during anaesthesia Any degree of hypoxia rapidly produces *per se* a sustained hyperglycaemia due to sympatho adrenal stimulation (Courville 1936) and is also undesirable in the presence of the type of vascular disease which is so common in diabetics because it may predispose either to cerebral or coronary artery thrombosis

Premedication

Although atropine has been shown to block insulin secretion produced by vagal stimulation (Portis 1950) and morphine can predispose to anoxia by respiratory depression the agents commonly used for premedication can usually be administered with safety

General Anaesthesia

Experimentally it has been shown that with ether and chloroform anaesthesia there is a breakdown of glycogen

(Brown and Long 1930) and in the case of ether this has been attributed to the fact that ether is a marked sympathetico mimetic agent and the effect being dependent on the consequent release of adrenaline In addition ether tends to cause vomiting *In the case of chloroform the toxic effect on the* liver is probably the important factor Both ether and chloroform are thus undesirable agents for general anaesthesia in diabetics Cyclopropane is a safer anaesthetic and causes only a slow rise in blood sugar though vomiting is sometimes induced (Robbins 1940) Foster and Francis (1955) have suggested that thiopentone induction with nitrous oxide and oxygen supplemented with minimal trichlorethylene pethidine or relaxants is probable the best method for most procedures

During such anaesthesia however they stress the importance of avoiding severe falls of blood pressure avoiding anoxia and carbon dioxide retention and maintaining adequate depth of anaesthesia to prevent sympathetic stimulation

Local and Spinal Anaesthesia

Local anaesthesia has only a limited use in *the surgical* treatment of diabetics This is especially to be noted in conditions affecting the feet and it should be emphasized that the combination of cocaine derivatives with adrenaline may be dangerous in the presence of peripheral vascular disease because thrombosis may be so easily precipitated in the smaller digital vessels

On the other hand spinal anaesthesia may be useful especially in the elderly patient requiring amputation of a limb and although the method is not widely used in this country it has been practised with success in other centres and notably at the New England Deaconess Hospital Boston (Joslin 195-)

Similarly there is no contra indication to the refrigeration technique in anaesthesia but hypotensive methods should be avoided because of the dangers of anoxia and the increased likelihood of inducing thrombosis

In summary it may be said that just as with so many other conditions which may affect the diabetic it is essential

to establish the closest co-operation between the various clinicians in charge of the case Once an understanding has been reached between the physician and the anaesthetist there should rarely be any difficulty in the management of the surgical diabetic case

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CHAPTER XVIII

THE LIVER AND GALL BLADDER IN DIABETICS

OVERPRODUCTION of glucose by the liver has been postulated as a cause of the hyperglycaemia in diabetics (Von Noorden and Isaac 1928) Catheterization of the hepatic vein in man however has revealed that there is no difference in the glucose output from the liver of normal individuals and diabetics (Bearn Billing and Sherlock 1951) Much recent research has been carried out into the role of the liver in the carbohydrate metabolism of normal and diabetic subjects but this is beyond the scope of the present discussion On the other hand there are a number of clinical associations between diabetes and the liver and the gall bladder which must be considered

HEPATOMEGALY

The liver is frequently enlarged in diabetics and in particular it is enlarged in badly controlled cases Goodman (1953) studied 459 patients and divided them into three groups 379 patients were well controlled 70 were poorly controlled and 10 had keto-acidosis Enlarged livers were found in 9 per cent of the controlled cases 60 per cent of the uncontrolled cases while all the ketotic patients showed hepatomegaly In particular it has also been stressed that children with badly controlled diabetes are especially liable to develop enlarged livers (Marble *et al* 1938) (See Fig XVIII 1)

The hepatomegaly tends to disappear with the establishment of good diabetic control and when it has been possible to examine such livers histologically it has been shown that the increase in size is due to fatty deposits and not to the abnormal storage of glycogen

Cirrhosis

There appears to be no increase in the incidence of cirrhosis in diabetics as compared with the non diabetic population Indeed Frankel found only 36 cases of cirrhosis amongst 3 543 diabetics and Joslin (1952) reports only 88 cases among 20 094 diabetics admitted to the George F Baker Clinic an incidence of 0 44 per cent which is less than the incidence of cirrhosis in the non diabetic population

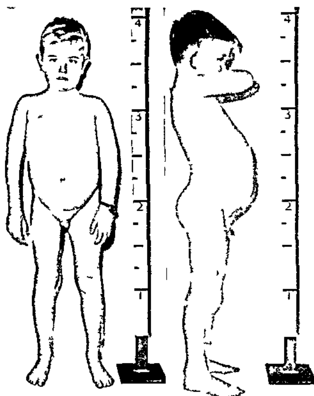


Fig XVIII 1 —Hepatomegaly in a poorly controlled child aged o yrs

HAEMOCHROMATOSIS

This is an inborn error of metabolism in which there is a slow accumulation of iron in the body (Sheldon 1935) It is usually associated with cirrhosis of the liver pigmentation of the skin gonadal atrophy and diabetes mellitus and this clinical syndrome was first described as bronzed diabetes by Hanot and Schachmann (1886) It is a rare condition and indeed Marble and Bailey (1951) were only able to trace 30 proven and 17 probable cases among 30 000 diabetics

The exact mechanism which causes the metabolic error is not known but tracer studies with radio active iron have shown that there is increased intestinal absorption of iron in haemochromatosis The diabetes which occurs in the fully developed case must be treated by diet and insulin where necessary and Lawrence (1955) has found that most cases eventually develop severe diabetes requiring large amounts of insulin to maintain normoglycaemia

CHOLELITHIASIS

Gall bladder disease with or without stone formation is common in diabetics particularly in the older age groups It is not possible to establish any true causal relationship and it may be that the same obese patients with hypercholesterolaemia who are liable to develop diabetes are also liable to develop cholecystitis and cholelithiasis In any event Lieber (1952) found that 30 2 per cent of all diabetics over 20 years of age have gall stones compared with 11 6 of the general population of the same age

The indications for cholecystectomy are the same as in non diabetics and complications are not especially liable to occur

An interesting but rare complication of emphysematous cholecystitis in diabetes has been reported by Tooms (1955)

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CHAPTER XIV

SKIN LESIONS IN DIABETICS

It is not uncommon for the presenting symptom of diabete to be related to the skin or at any event to ectodermal tis sues Thus pruritus vulvae is the commonest presenting symptom in middle aged women while generalized pruritus may also occur sometimes without heavy glycosuria and without grossly elevated blood sugar levels An infective skin lesion may be the presenting symptom and many patients with pruritus vulvae are found to have an associated monilial vaginitis The rare condition of necro biosis lipoidica diabeticorum may also occasionally lead to the diagnosis of diabetes In addition to these conditions which may occur as a manifestation of diabetes there are certain local skin reactions to insulin administration which must be regarded as complications of treatment

Skin Infections in Diabetics

Boils and Carbuncles Such conditions as boils carbuncles axillary abscesses and ischio rectal abscesses are common in diabetics and the old rule that any patient attending casualty with a boil or carbuncle should have the urine examined is fully justified Indeed it has been shown that about 20 per cent of cases of diabetes are discovered as the result of a septic skin lesion (see Chap IV p 44)

Treatment is on the same general principles as in non diabetics local treatment and appropriate antibiotic therapy both being required Pending the isolation of the responsible organism and its sensitivity to antibiotics the most satis factory antibiotic is penicillin—preferably given in the crys talline form in two daily doses of 500 000 units Prompt con trol of the infection is important as the diabetic state may be difficult to control until this is achieved and at the same time it is important to control the diabetes because hyper

glycaemia appears to favour the persistence of septic conditions

Pruritus Vulvae and Monilia Pruritis vulvae may be one of the most intractable conditions in diabetics and when it persists after the control of glycosuria it is usually due to the presence of a monilial vulvitis There is usually extreme itching and irritation of the vulvae with an acutely inflammed vulvar and peri anal skin showing a well defined edge to the lesion a macerated superficial epithelium and sores caused by scratching In 15 cases described by Barr (1957) having the above appearance C Albicans was demonstrated in all cases in the superficial epithelium of the vulva Some diabetics complain also of a discharge when it has the characteristic white curd like or caseous appearance

The diagnosis may be confirmed by the microscopical examination of smears and by the inoculation of Nickerson s medium incubated at room temperature for five days (Barr 1957)

Even though positive proof is lacking and certainly whilst awaiting laboratory confirmation it is justifiable to prescribe 1 per cent aqueous gentian violet paint In recent years Nystatin has been found to be effective against the fungus disease It was discovered in 1950 by Hazen and Brown (1950) and acts by inhibiting cell division and mycelial growth Since then there have been many reports in the literature of its efficiency in treating moniliasis of the vagina Barr (1957) recommends giving local treatment as an ointment containing 100 000 units of Nystatin per G of emulsifying ointment B P base applied to the affected parts twice daily for two weeks Also the patient inserts two vaginal tablets of 100 000 units each night She is told not to wash the vulva with soap and water but to cleanse the skin with warm olive oil Oral tablets were thought to be unnecessary

Symptomatic relief from persistent pruritus vulvae sometimes follows the application of 1 per cent hydrocortisone cream

Intertrigo Diabetics and particularly obese females are liable to develop intertrigo under the folds of the breasts at

the umbilicus and in the axillae groins and natal clefts Such intertriginous lesions are also liable to become secondarily infected with monilia and unless this is recognized and appropriate treatment instituted the intertrigo is likely to be very persistent The surfaces may be separated by a few layers of gauze smeared with 10 per cent gentian violet in zinc cream or painted with Castellani s fuchsin paint and then dusted with zinc oxide and talc powder with or without 3–5 per cent salicylic acid fine powder (Roxburgh 1955)

Epidermophytosis Interdigital fungus infections are common in diabetics and unless promptly treated may well lead to more extensive infection of the feet and in subjects with peripheral disease such lesions may occasionally be the precipitating cause of gangrenous lesions

Local Reactions to Insulin

Fabrykant and Ashe (1953) have classified the various local reactions to insulin as follows

(1) Inflammatory lesions consisting of itching stinging or burning tenderness redness and swelling These appear from a few minutes to 12 hours after injection and subside in 1–7 days

(2) Painless subcutaneous indurations which develop in repeatedly used insulin sites and persist for weeks

(3) Lipodystrophies These may take the form of deep concavities from loss of subcutaneous fat and are covered by a pale insensitive skin often adherent to the underlying structure (See Fig XIX 1) Alternatively they may take the form of painless swellings of spongy consistency covered with thick and easily movable skin There is a wide variation in the reported incidence of local reactions to insulin other than the lipodystrophies Indeed Allan and Scherer (1932) found that different workers reported incidences varying from 32–84 per cent

Fabrykant and Ashe (1954) found that in a group of 100 sulin treated diabetics 25 per cent of patients were con tently free from local lesions while the remaining patients ubited such lesions for up to 31 years of insulin therapy

This high proportion of patients developing lesions greatly outweighs the average incidence of 10 per cent of allergic disorders in the population as a whole thus suggesting that factors other than hypersensitivity to insulin are responsible



FIG XIX 1—Lipoatrophy at site of insulin injection abdominal wall and thigh

for the development of these lesions Furthermore Gelfand Fabrykant and Ashe (1954) failed to find any significant difference in skin tests between diabetics affected with local skin lesions and non diabetic controls It seems however that the occurrence of local reactions may be related to the manner in which insulin injections are made The incidence appears to be highest when the injection does not ensure de

position of insulin in the deepest layers of subcutaneous tissue and it is significantly smaller in those who insert the needle deeper by thrusting it straight into the skin and by those using an automatic syringe The daily shifting of the site also appears to be important in reducing the incidence of local reactions Such a local reaction may follow the use of any type of insulin and although it was at first hoped that the insulin zinc suspension might have been less likely to cause reaction than the older long acting zinc insulin which contained a foreign protein (*Brit med J* 1953) it has never theless been found with the increased use of these preparations that the well recognized local lesions may occur (Mason and Veral 1953 Murray 1954 Armstrong and Lloyd 1954 Davidson 1956) Lipodystrophy either in the atrophic or in the hypertrophic form is less common and of the two types lipoatrophy is better recognized

Yohalem and Pollach (1949) found lipoatrophy in 33 3 per cent of adult diabetic patients and Paley (1953) found a 54 8 per cent incidence of lipoatrophy in a series of patients attending the diabetic clinic at the General Infirmary at Leeds The complication was significantly more frequent in female than males

Various factors have been suggested as causation and these include the preservatives used in manufacture of insulin the alcohol used in sterilizing syringes and needles local sensitivity to insulin injury of nerve fibres and chemical injury of the subcutaneous fat

None of these factors have been conclusively implicated and Paley (1953) points out that it has not been possible to produce atrophic lipodystrophy experimentally in animals On the other hand he did find that it occurred more commonly in patients on protamine zinc insulin than on crystalline insulin and it seems possible that an impurity in the injected insulin may possibly be the lipolytic agent

Because the exact cause of the abnormality remains unknown no rational therapy is available although Paley found that in almost 30 per cent of cases there was a spontaneous improvement irrespective of treatment

Necrobiosis Lipoidica Diabeticorum Necrobiosis lipoidica

diabeticorum was originally described as a complication of diabetes and the name was suggested by Urbach in 1932

The lesions appear most commonly on the lower extremities as papules or plaques yellow in the centre with red slightly raised edges showing telangiectasia and later atrophy and sometimes ulceration Histologically areas of necrobiosis were found in the middle and deep thirds of the cutis thought to be caused by obliterative changes in the dermal vessels but a connection with the disordered fat metabolism in diabetes was suspected for several years (Hare 1955) Later cases were described in persons without diabetes or in whom diabetes has not developed after a number of years

Other conditions with similar clinical or histological appearances have been described but at present there appears to be insufficient evidence to show if there is a common aetiology

Treatment Improvement in the lesions in up to 90 per cent cases by injections of cortisone have been described (Savitt 1955)

Xanthoma Diabeticorum Xanthomatous tubercles occasionally occur in diabetics They are most common on the outside and back of the forearm and may become confluent about the elbows and knees It is thought that the condition is associated with lipaemia and in 12 cases observed by Joslin (1947) the average blood cholesterol level was raised to 756 mg per 100 ml

No specific treatment other than good diabetic control and possibly reduction of animal fat is indicated

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PART III

MEDICO SOCIAL ASPECTS OF DIABETES

INTRODUCTION

The isolation of insulin was one of the greatest achievements in medicine On the other hand because insulin is not a cure for diabetes but merely a means of controlling it there is now a growing population of life long diabetics The population is growing not only because individual diabetics are living longer but because these people are rearing children some of whom are also likely to become diabetic or pass on the disease

Apart from supervising the medical care of diabetic patients it should be the aim of all doctors in charge of diabetics to try and help their patients to live as normal and full a life as possible and it is with regard to the many medico social problems that inevitably arise in this connection that this section is concerned Firstly the various social factors that are important in the different age groups are considered secondly the functions of the diabetic clinic are discussed and finally the work of the Diabetic Association is briefly described

CHAPTER XX

PROBLEMS OF THE DIABETIC LIFE

To a large extent the social problems vary according to th age of the patient and the various age groups will therefor be considered in turn

1 **Diabetes in Childhood** Diabetes though relatively rar in childhood creates many problems when it occurs In survey of 1 307 000 schoolchildren under the age of 16 Henderson (1949) found 183 known diabetics an incidenc rate of 1 in 7 000 The incidence rose sharply from 1 in 180 000 for children under 5 to 1 in 180 000 for 5–9 years an 1 in 300 for children from 10–15

When the child is very young at the onset the chief burden falls upon the parents and in many cases the management of the case is complicated by the serious psychological impact that its development has upon the mother Indeed it is often more difficult to treat the parents of diabetic children than to treat the patients themselves Dietary restriction is diffi cult to impose on young children but unless they are edu cated in some form of carbohydrate restriction at the onset of the disease it is difficult to persuade them to accept it later Insulin is always required in juvenile diabetics and the sooner they are able to give their own injections the better and most children should be able to give their injections by the age of 10 A number of automatic jet injectors are available such as the Palmer injector (See p 125)

It is essential in the management of juvenile diabetics that they should be able to take part in all the activities under taken by non diabetic children of similar age and in this respect it is the adjustment of the diet and insulin dose prior to exercise which requires careful study It will be found that the requirements vary from patient to patient and for different types of exercise Thus Kennedy (1955) states that one juvenile diabetic had found by trial and error that an average set of tennis demanded an extra 15 G carbohydrate

with a 5 gm variation either way according to whether the set was strenuous or mild. Particular care is obviously required when diabetics are taking part in sports where a hypoglycaemic reaction could have serious consequences. Swimming and riding are obvious examples, but each case has to be considered individually and it must be the constant effort of the patient's physician that the minimum of restrictions are placed upon the juvenile diabetic's activities.

Stress is often laid by psychiatrists upon the danger of young diabetics being made to feel different from their contemporaries and upon the dangers of inducing a guilt complex if they are found straying into the food cupboard or indulging in the chocolate box.

So long as these points are borne in mind by the physician all should be well, but the fact cannot be ignored that these children are different from normal children, but far less different than before the days of insulin when the difference was that they died, whereas they may now live diabetic lives. A full recognition of this point should help the physician, his patient and the patient's parents to view the problem in its right perspective.

Hostels for Diabetic Children. Hostels for diabetic children are run by such authorities as the London County Council, the Church of England Children's Society and Dr Barnardo's Homes.

It should only rarely be necessary to remove diabetic children from their home environment, but there are occasions when it is better to do so. Tunbridge (1953) points out that the difficulty of controlling satisfactorily the juvenile diabetic is especially great when a child comes from a home that is poor economically, emotionally or morally. Henderson (1949) has also reviewed the type of case where hostel accommodation is better than the home, and in his survey found that about one diabetic child in nine was recommended for a hostel. In many cases the children were orphans or had parents who were separated and in London the effect of wartime bombing increased the proportion of cases where home accommodation was unsuitable. He concluded from his survey that there was a need for hostels for 130–150 diabetic

children under 16 years of age in England and Wales with a school population of 5 million

Camps for Diabetic Children In the United States there is great enthusiasm for diabetic holiday camps and Marble (1952) considered that the primary aim of the camp should be to show diabetic children that they can take part in the activities of a normal child and that with reasonable attention to diet and regularity of meals and insulin injections they can live as ordinary children

In this country the Diabetic Association has organised similar camps for diabetic children and although these have been on a smaller scale than those in America they have always proved both popular and successful More recently the Association has embarked on a further project and now runs holidays abroad for parties of diabetic children

2 **The Adolescent Diabetic** There are a number of specific problems that occur in adolescent diabetics First the diabetic state may become rather labile This is possibly because of the increased hormonal activity and particularly in girls there is often associated with adolescence a marked increase in the insulin requirement At the same time the adolescent begins to assert himself or herself and demands an increasing degree of independence Unless the patient fully understands the importance of maintaining good diabetic control a difficult situation can easily arise with a sense of resentment at the restrictions of a diabetic life and a renewed unwillingness to accept the discipline of diet and regular insulin therapy This is also the age when the patient's career is being planned and it is essential that suitable employment shall be found Work carrying special hazards must clearly be avoided and diabetics are not accepted in the Armed Services

The Youth Employment Bureau may be able to help and the vast majority of juvenile diabetics will find suitable work There will of course always be a number of cases who are difficult to place but these are usually those with a low I Q in whom the diabetes is poorly controlled

3 **The Diabetic Citizen** The aim of the physician in charge of adult diabetics should be that men and single

women should be able to earn their livelihoods and that married women should be able to fulfil the normal duties of motherhood and housekeeping

The Employment of Diabetics This is clearly the most important social problem which affects adult diabetics Mild diabetics and especially those taking no insulin present no employment difficulties Severe diabetics may present difficulties and the unco operative uncontrolled case is liable to prejudice employers against all diabetics Certain criteria have been suggested by the American Diabetes Association regarding the employment of diabetics in industry (Editorial *J A M A* 1954) The following are the more important of the standards laid down

(1) A diabetic seeking employment should present a note from his physician stating he is controlled and under goes periodic examinations
(2) Diabetics can perform any work for which they are equipped physically mentally and educationally Those taking insulin in large doses should not be assigned to work where hypoglycaemic attacks would injure either them or others
(3) Where possible diabetics should work straight shifts (unbroken and non rotating) If a rotating shift is necessary they should avoid the one between mid night and 8 a m This is the only concession in terms of hours that a well controlled diabetic should ask
(4) Certain key personnel in a plant employing diabetics should be familiar with the nature of diabetes and the possibility of coma or insulin reactions
(9) Diabetics should carry cards identifying their con dition
(6) Each diabetic should have a complete annual physical examination
(7) Transfer or reassignment of a diabetic at the request of the industrial M O when new complications create new risks is a justified procedure

Beardwood (1950) believes that a well educated and well controlled diabetic is to be regarded as a normal individual

as far as his activities and mode of living are concerned and that the basis on which diabetics should be employed should be the job suitability of the individual and the degree of co operation he extends to his physician He believes that the careless diabetic is also the careless workman although the good diabetic has frequently proved his worth This was well illustrated in a review by Brandaleone and Friedman (1953) These workers analysed replies received from 63 companies regarding working time lost amongst a total of 780 823 employees Two companies found that diabetics lost less time than non diabetics 44 companies reported no difference between diabetics and non diabetics while in the remaining 17 companies the information yielded was in determinate

Most diabetic workers are over the age of 40 and are valu able employees because of their long service and experience and the majority of workers who become diabetic do not need to change their jobs On the other hand the danger of insulin reactions must be constantly borne in mind and in particular no diabetic should be in a position where as a result of an insulin reaction he would endanger the lives of others as well as his own

Beardwood (1950) mentions the driving of public transport vehicles the piloting of aircraft the manipulation of cranes and scaffolding as specific examples of occupations which should not be carried out by diabetics taking insulin

The successful employment of diabetics in industry obvi ously requires co-operation both on the part of the employer and the employee

An unfavourable attitude on the part of management only leads to concealment of the disease discouragement and dis content resulting in a higher rate of unemployment Like wise the employee must be taught that his disease properly cared for does not pose a problem in industry and this can be brought about by close co-operation with his own physician and the industrial medical officer

Driving Motor Vehicles A diabetic patient who has an accident as a result of an insulin reaction is liable to be convicted for driving the vehicle while under the influence of

drugs (*Brit med J* 1957) Furthermore a diabetic taking insulin who is liable to sudden hypoglycaemic reactions or a patient who does not accurately recognize symptoms of hypoglycaemia should not apply for a driving licence In deed in completing his application form he cannot conscientiously state that he is not liable to blackouts in answer to the specific question on this point

Having said so much it must be admitted that motor accidents rarely occur as the result of hypoglycaemic attacks and that the majority of diabetic drivers are as safe as most non diabetics

The Diabetic Association has urged all doctors in charge of diabetics taking insulin and driving motor vehicles to ensure that their patients understand the possible cause of hypoglycaemia and also appreciate the consequence of a severe reaction while in charge of a vehicle They should always carry an emergency supply of carbohydrate while driving

Life Insurance Since it has been shown that insulin has so greatly increased the longevity of diabetics a number of Life Offices now quote reasonable terms for diabetics although premiums higher than normal are usually charged The Mercantile and General Reinsurance Company Limited operate a pool for the reassurance of diabetic risks and a number of the Life Offices avail themselves of this service

The patient's own doctor will be required to give a report to the insurance company and it is required that the patient is well stabilized and under proper medical supervision in a diabetic clinic In addition to the ordinary proposal form a special diabetic questionnaire must be completed with information regarding the patient's diet insulin dose and the duration of the disease Complications especially albuminuria and hypertension should not be present

The Elderly Diabetic In the past it has sometimes been thought that diabetes in the elderly is a mild condition That this is an erroneous view has already been stressed and many elderly diabetics require large doses of insulin in addition to their diet to keep them out of keto-acidosis Furthermore it

must again be stressed that this complication is particularly to be avoided in the elderly because of the difficulties of restoring the fluid and electrolyte balance in a severely dehydrated elderly patient with a poor circulatory system

Good diabetic control is therefore as important in the elderly diabetic as it is in younger age groups

There are however special obstacles to the attainment of this ideal First the patients are often disabled on account of their age and find regular attendance difficult either at the diabetic clinic or at their own doctor s surgeries Secondly they are often unreliable because of cerebral arteriosclerosis and tend to be inaccurate both in keeping their diet and in their insulin administration while failing vision is another factor often responsible for inaccurate insulin dosage Economic factors may also make it difficult for elderly patients to follow their diets strictly because a diabetic diet tends to be costly at any rate during certain times of the year

All these difficulties must be appreciated by doctors in charge of elderly diabetic patients

The help of the District Nurse in insulin administration may often be required although it is difficult for the district nurse to ensure that the insulin is given at the same time each day and it is more satisfactory if a relative undertakes the responsibility of giving insulin The home help service is also valuable in providing domestic assistance and sometimes in the preparation of meals In some districts a Meals on Wheels Service is available and will provide diabetic diets

Finally there are those elderly diabetics who are unable to live alone and must be accommodated either in chronic sick wards or in welfare accommodation The majority of local authorities state that they raise no objection to providing special diets for diabetic patients although some welfare officers are still rather unwilling to accept diabetic patients In January 1953 The Frederick Banting House was opened in Kingston Surrey for elderly diabetics with accommodation for about 30 residents It is run by the Diabetic Association and it is hoped that further similar homes will be opened in the future

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CHAPTER XXI

THE DIABETIC CLINIC

THERE are some physicians who still believe that diabetes should be regarded as a general practitioner disease and that once a patient has been stabilized he should be returned to his family doctor for all further supervision and care There is perhaps much to be said for this point of view but it fails to take certain difficulties into account Firstly the number of diabetics in individual practices is rarely large enough for many doctors to be enthusiastic in the regular follow up of their cases secondly few family doctors have facilities for blood sugar estimations and thirdly there are many doctors who will frankly admit that they cannot keep abreast of the modern trends in diabetic treatment although some practitioners feel that they will be even less inclined to keep up with modern treatment if the diabetic clinic takes over their cases The majority of general practitioners are delighted for their diabetic patients to make regular visits to the diabetic clinic If there is good liaison between the clinic and the G P the latter will be kept well informed both about the progress of his patient and of modern developments In order to maintain such a liaison it is helpful if the general practitioner receives a brief report on the patient s diabetic state after each clinic attendance This may throw an additional burden on the hospital staff but if a simple proforma is used as in Fig XXI I the minimum of relevant information may be passed on and this is greatly appreciated by general practitioners

The functions of a diabetic clinic may be considered under two main headings—first the care and education of the patients and second the conduct of clinical research and the post graduate education of the doctors and their assistants

1 **The Care and Education of the Patients** The care of the patient is clearly the first object of the diabetic clinic and it has two distinct aspects Firstly there is the maintenance

of good diabetic control and secondly the education of the patient and the management of the medico-social problems already discussed

> Dear Dr
>
> Your patient
>
> attended the Diabetic Clinic on
>
> The degree of control is
>
> Urine examination revealed
>
> Blood sugar estimation was
>
> Insulin dose advised
>
> Next Clinic attendance
>
> *REMARKS*

FIG No 1

Whenever possible new patients should be stabilized as out patients but in special circumstances it is more desirable to admit them for stabilization In the clinic the staff must instruct patients in such routine matters as urine testing and insulin administration although most patients require the assistance of their district nurse in this matter in the early stages

Ideally there should be a senior member of the nursing staff—*permanently attached to the diabetic clinic*—but this

is often difficult in hospitals where there is a shortage of *nursing staff*

Dietetic Advice A dietitian should be available in the diabetic clinic and the medical and nursing staff should also be familiar with the carbohydrate value of the common foods *so that they can advise patients on simple dietetic problems*

In some clinics the dietician or catering officers are helpful in arranging simple demonstrations

Almoner Service An almoner should be available in all clinics to advise *patients on the many social problems* that may occur She should be familiar with the particular problems likely to befall diabetics and aware of the various facilities such as convalescent homes homes for the elderly diabetics and other similar services

Chiropodist A chiropodist service should be available in all diabetic clinics but it is vital that the chiropodist is specially trained and aware of the potential dangers to the feet of diabetics All diabetics should be instructed in the clinic about the importance of the care of their feet (see *Chap* XII) and should be warned against the dangers of having their feet treated by unskilled chiropodists

Routine Clinic Visits When a patient is well stabilized it should not be necessary for him to attend the clinic more frequently than once in three or four months Every patient should be thoroughly examined and reviewed on at least one of his attendances each year and an annual chest X ray should be carried out

All diabetic patients taking insulin should carry a card indicating that they are diabetic and stating the insulin dose The specimen card shown in Fig XXI *2* is that issued by the *Diabetic Association*

2 Research and Training of Doctors *Although certain* types of scientific research *especially* those requiring laboratory facilities can only be carried out in the larger centre *every physician in charge of a* diabetic clinic should be able to study some clinical aspect of the condition

As already stressed the patients attending diabetic clinics form an ideal population in whom to study the natural history of disease because many become life long attenders and

indeed it is not uncommon to find members of several generations attending the same clinic

There are many opportunities for clinical research in a diabetic population but if any project is to be successful it is

IMPORTANT

The bearer of this card is a diabetic and takes Insulin In the event of sudden confusion or faintness please give 2 full tablespoons of sugar in water and get the nearest doctor at once

P T O

ISSUED BY THE BRITISH DIABETIC ASSOCIATION
152 HARLEY ST LONDON W 1
Ph WELBECK 6001 0556

NAME
ADDRESS

FAMILY DOCTOR Phone
DIABETIC CLINIC Phone
Phone

INSULIN Type
UNITS { MORNING
EVENING

FIG XX

INDEX